PERIPHERAL CIRCULATION
IN MAN

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A CIBA FOUNDATION SYMPOSIUM

PERIPHERAL CIRCULATION IN MAN

Editors for the Ciba Foundation

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PREFACE

THE Ciba Foundation is an international centre established as an educational and scientific charity under the laws of England It owes its inception and support to its founder *Ciba Limited of Switzerland* but is administered *exclusively* by its distinguished Trustees

As one part of the Foundation s activities informal symposia or colloquia strictly limited in membership are arranged to which leading research workers from different countries and different disciplines are invited As the small ness of the group necessarily excludes many others active and interested in the subjects discussed the proceedings are being published and made available throughout the world

Peripheral Circulation in Man was the subject of a symposium arranged in succession to one held and published earlier on *Visceral Circulation* It was largely initiated by Prof A C Burton Prof J H Dible and Dr O G Edholm to whom the Director of the Foundation is greatly indebted for support and advice in its organisation

The book covers the methods for studying blood flow the changes in circulation due to exposure to cold or heat the actions of adrenaline and noradrenaline on blood flow the neurohistology and reflex control of the circulation and the effects of sympathectomy the significance of cold agglutinins and *the influence of visceral activity on the peripheral* circulation

To an understanding of these problems important workers in this field whether anatomist physiologist biophysicist pathologist physician surgeon or in aviation medicine have contributed

It is hoped that the papers and discussions presented here will prove not only informative and stimulating but will also give a sense of participation in this informal and friendly occasion

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List of those participating in or attending the Symposium on The Peripheral Circulation in Man 11th 13th May 1953

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CHAIRMAN S OPENING REMARKS

O G EDHOLM

THE purpose of this Symposium is to make it possible to have a more lengthy discussion than can usually be arranged at meetings of the learned societies There is a rapidly growing activity in the field of human physiology and particularly in studies of the peripheral circulation It is certainly important that workers with common interests should have the *opportunity of discussing their results together*

Human physiology is still regarded with some suspicion by a number of physiologists Perhaps one reason is that research on human physiology has its own special difficulties It is harder to work on man than on isolated pieces of tissue for several obvious reasons These include the necessity for strict control of the environment and even more important for controlling the conscious subject There are many factors which can influence the peripheral circulation in man most of which are still poorly understood and therefore hard to control It is not always easy to obtain subjects with the frequency and regularity that one would desire and owing to the length of time usually necessary to carry out an experiment there is always a relatively small output of work For these and other reasons the results of human physiological research are not always as clear cut as in animal experiments and it must be admitted that some work has not been done as carefully as it might have been However work in recent years a high proportion of which has been contributed by those present at this Symposium has established the importance of research on the circulation in man It has been shown that satisfactory work can be carried out on man and the results of such work demonstrates that it is not always possible to apply the findings of animal experiments to man

One important aspect of work on the circulation in man is that this is a most fruitful field for the collaboration of physiologists physicians pathologists and surgeons It is a field in which the results of clinical work are of great importance to physiologists Problems are revealed which would otherwise be unsuspected by the physiologists In this Symposium there is a balance between the clinical and physiological aspects both as regards membership and papers

It is not possible in a brief introduction to give any picture of the problems of the peripheral circulation in man except perhaps to emphasize the extent of our ignorance It may appear to those who are not engaged in this field that the circulatory system is relatively simple compared to many other aspects of physiology We are in fact still unable to define with precision the laws governing blood flow in vessels and all the factors governing dilatation and constriction

I hope we shall shed a little light on these and other aspects in the course of this Symposium

A CRITICAL SURVEY OF METHODS AVAILABLE FOR THE MEASUREMENT OF HUMAN PERIPHFRAL BLOOD FLOW

ALAN C BURTON

Introduction

A GREAT number and variety of methods have been devised for the measurement of blood flow in fragmented and anæs thetized animals of which only a few are at all applicable to intact unanæsthetized animals Knowledge of the peripheral blood flow in the relatively undisturbed and intact animal made possible in the human largely because of the co operation of the subject is so valuable that a critical survey of these few methods is very worth while All methods that have been used have some merits and all have disadvantages In some cases we will never agree on these relative merits nor should we for any given method may be the best for one experi menter in the circumstances of his particular research yet not as good for another worker The methods should be regarded as complementary and not as rivals as it is only by the knowledge of the results of all the methods each with its own peculiarity that we shall be able to synthesize the true picture of the peripheral circulation

It has been the custom to classify methods of measurement as direct and indirect To do so we must first perhaps arbitrarily define precisely what it is that we wish to measure which a direct method will give us For the purposes of this critical survey it is assumed that the object of our direct interest is the volume flow of blood in ml /minute rather than the velocity of flow in cm /second or some related quantity This seems a reasonable definition of aim since the major function of the circulation is to supply the metabolic needs of the tissues and the volume flow is closely related to

this Thus by definition here the target variable" is the volume flow of blood Whether or not we should express this in total amount or per 100 ml of tissue or perhaps per sq M of surface area is a matter too inconclusive to discuss here

If we then decide that a method is absolutely direct if it yields this target variable without intermediate steps involving other variables we shall have to agree that almost all available methods are indirect though "direct' if we had chosen some other target variable' (such as effective thermal conductivity amount of hæmoglobin velocity of blood flow etc) It seems better to abandon the classification into 'direct and indirect and ask three questions about each method —

(A) What quantity or quality of tissue is directly measured by this particular method? We might call this the *intrinsic variable of the method*

(B) What is the relation of this intrinsic variable to the target variable ' i e the volume flow of blood? What other variables are involved in this relation and thus affect the measurement? We might call this relation the *intrinsic correlation of the method*

(C) How greatly does the application of the method of measurement disturb the pre existing condition of the organism so that though the intrinsic variable of the method is correctly reported the undisturbed volume flow of blood cannot be deduced? This last question is all important to physiologists yet it seems to be this question that is least asked In the day of Claude Bernard it was in the minds of all biological scientists for in his Introduction to the Study of Experimental Medicine he tells us of the school of thought that contended that no experiment on a living organism could be useful because by application of the measurement the organism was profoundly disturbed Yet today I cannot find even a well established term for this type of error of measurement I would suggest we call it the '*Reactive Error in Physiology* since it is due to the reaction of the organism to the stimulus of the application of the method of measure

ment Because of this 'reactive error' there is a biological 'uncertainty principle that is often of much more practical importance than that of Heisenberg in Physics (which points out that even the velocity of an electron is distorted by the act of observing it which can only be done by introducing radiation)

Let us examine the methods available for the measurement of blood flow in man by asking these three questions which, in the terms I have defined are concerned with —

(A) The nature of the intrinsic variable of the method

(B) The intrinsic correlation of the method with the target variable i e volume flow

(C) The reactive error of the method

In addition of course there are the other important properties of any method of measurement such as speed of response or lag' and the sensitivity to changes in the target variable (volume flow of blood) For detailed and critical discussion of each of the methods the articles in Methods of Medical Research (1948) should be consulted

Specific Available Methods

Direct Observation of Blood Vessels

There are growing opportunities for this in the human The specialized capillary bed at the base of the finger nails is no longer the only area for observation The vessels of the tongue have been used with modern methods of microscopy and of illumination by cold light which will not introduce a large reactive error The use of fluorescence improves the contrast between tissue and blood vessels for observation

There is a natural tendency to assume that when one actually sees the blood vessels this must be the most certain and direct of all methods for study of the circulation For some target variables it may be so but is it so where we desire the volume flow? What is the intrinsic variable of the method of direct observation? My own conviction is that

it is probably the velocity of movement of the erythrocytes that dominates the impressions of the observer and his judgment as to whether flow has increased or decreased When however the diameter of the vessels observed changes at the same time as the velocity of the erythrocytes the volume flow cannot be in any sense the 'intrinsic variable' Volume flow is the product of the mean velocity of flow at the point of observation and the cross sectional area there

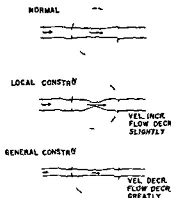


Fig 1 Schematic diagram to illustrate the relations between velocity of flow and volume flow

and where both change the intrinsic correlation is very complicated For example (Fig 1) if a narrowing of the vessels under observation occurs which is greater than elsewhere in the line of vascular resistances the volume flow will decrease Yet because of the reduced cross sectional area at this point the velocity of flow here will increase On the other hand in a more severe and widespread vasoconstriction the volume flow will decrease greatly and in this case velocity of flow also will decrease I think this is why we find in our undergraduate laboratory experiment on observation of flow in the web of the frog that students are unable to decide whether the topical application of adrenaline results

in an increase or a decrease in volume flow (Most of them decide that there has been a vasodilatation)

As far as ' reactive error is concerned this might be considered negligible as long as the illumination or the application of immersion oil or the pressure of the applied apparatus does not affect the circulation Where a drug is used such as adrenaline we are of course interested in the disturbance of circulation by that drug but here we should consider whether this disturbance is identical with the physiological disturbance by that drug A great body of theory as to the circulation in shock has been based upon direct observation of the reaction of minute vessels to topically applied adrenaline (by Chambers Zweifach and others) Can we be sure that the reaction of vessels would be the same to topical application as to the physiological presence of the same hormone in the perfusing blood in view of its very rapid destruction by the enzymes in the vessel walls? Certainly gradients of reactivity of different vessels found by topical application would be very different from the physiological gradients This is a case of reactive error of measurement of a more complicated kind

Circulation Time

The ingenious classical methods using injected dyes or electrically conducting saline or substances that signal their arrival by effects on special receptors (e g taste or smell) have been superseded by the use of radioactive tracers whose arrival is so easily detected by counters With the improved techniques of arterial injection it is now feasible to measure circulation time in a limb as well as total circulation time

The answer to the first of our three questions is deceptively simple The intrinsic variable is the time in minutes or seconds for the injected substance to circulate from point A to point B But we need to be cautious A recent analysis of just what is measured has been made (Pearce Lewis and Kaplan 1952) Even where a slug of injected substance is very rapidly injected the sharp rise of concentration of the wave front does not persist and it is not the arrival of the

first amount that is measured but of the *first detectable* amount Thus the authors found that the injection of a 80 per cent solution of Decholin (taste as the end point) gave a circulation time 15 per cent shorter than with a 10 per cent solution If we should decide to use the arrival of the peak of concentration instead of the least detectible amount we are in similar difficulties because of the change in shape of the curve as the dye circulates

As to the intrinsic correlation for the circulation time, it is most important to realize that the circulation time from point A to point B of the vascular bed is equal to the volume of the

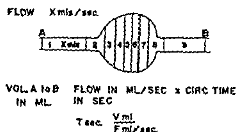


FIG 2 *Diagram to show the relation between circulation* time T volume flow F and the volume of the vascular bed V

vessels between A and B divided by the flow (Fig 2) *It is* astonishing how this elementary fact has been ignored in the past Since changes in flow are produced by constriction or dilation of the vessels and also since changes in volume *will* result from any redistribution of pressures due to a vasomotor change it is inevitable that both factors of the ratio for the circulation time (volume and flow) change simultaneously *In general* but not inevitably the volume will increase as the flow increases and thus the circulation time is remarkably insensitive as an index of flow or of vasomotor change The *intrinsic correlation is thus very poor* Indeed *it is possible* during a vasoconstriction that the volume might decrease so greatly as to *offset completely* the decrease of flow and that

the circulation time might actually decrease Certainly any change in circulation time is as likely to be due to a change in volume of the vascular bed (called the pooling effect by Ziegler 1951) as to change in flow It is no wonder that few physiologists know quite what to do with circulation time after it has been measured I know of no attempt to preserve the usefulness of the circulation time by measuring the change of volume of a limb at the same time and so calculating the change in flow This might be a useful addition to our methods

As to reactive error with any method using arterial injection the possible disturbance of the *status quo* even with small catheters must be considered If no local anæsthetic be used the artery may go into spasm and the psycnic effect of pain may be great Even the anticipation of an arterial puncture can produce a very marked general vasoconstriction On the other hand if local anæsthetic be used the vasomotor tone we wish to measure will be reduced to an unknown extent In addition there are physical reactive errors especially with fine catheters and recording with rapid instruments that have not been sufficiently appreciated

Injection (dye) Dilution Methods or the Use of the Fick Principle

As I have no experience of these I can only point out the difficulties of them which are well known The chief difficulty is that of obtaining a representative venous sample because of the collateral arrangement of the blood vessels of a limb In acute animal experiments the collateral circulation can be occluded but obviously this is not possible in the human limb where Edholm and his colleagues (1951) have shown its importance This would appear to exclude these methods for the estimation of human peripheral circulation The same reactive errors exist as for any other method involving arterial catheterization or injection

A disadvantage (of a different kind) of some of the Fick methods applies to the nitrous oxide method (Kety 1948)

used successfully for brain flow in man and for coronary flow in animals This is that not the absolute flow but the flow per 100 ml of metabolically active tissue is measured If some tissue is without blood flow, but also inactive in taking up the foreign substance the result for flow with such methods may be normal For example a complete lack of correlation has been found between cerebral symptoms and the measured flow in cerebral damage from hypertension (Bessman, Alman and Fazekas 1952)

Clearance Methods

Kety has also been a pioneer in measuring the clearance of radioactive ^{24}Na or ^{131}I from tissue as an index to the blood flow The method which has been used in this country by McGirr (1952) and by Miller and Wilson (1951) seems delightfully easy to apply to human peripheral circulation A small amount of radioactive ion is injected into the tissues and the rate of clearance from the area is then followed by a counting device Most of those who have used the method are well aware that blood flow is not directly measured and that the permeability of the tissue blood barrier is also involved It would seem safe to assume in many experiments that this permeability factor remains constant but only comparison with flow measurements made directly can settle *the matter Measurements of clearance from muscle by this* means however have already shown differences from results for flow more directly as for example with adrenaline where the increase of muscle flow found by Barcroft does not seem to correspond with an increased clearance (Miller and Wilson 1951) As with circulation time most valuable results might follow from the simultaneous use of two methods in the same test in this case of the clearance of muscle and of the blood flow by the classical plethysmographic method

Sometimes the semi logarithmic plot of decay does not give straight lines but curves This has been attributed to the contributions of two clearances from muscle and from skin at different rates and it is claimed that these can be separated

in the graphs by drawing initial and final slopes (Wisham and Yalow 1952) Warning must however, be given that such an assumption is not at all mathematically sound unless the curve is very definitely linear over a considerable range at each end of the graph and the curvature is in the middle portion only Otherwise the initial and final slopes may still be a great admixture of the two underlying clearance rates

These methods of radioactive clearance undoubtedly will have great application to the study of peripheral vascular disease because of their ready clinical application They add one more weapon to our armament the full value of which will result from the realization that the intrinsic variable here is not the same as with other methods

Skin Colour

This valuable index of the state of the circulation was adequately discussed by Sir Thomas Lewis It depends mainly on the volume of blood (rather than on blood flow) and its state of oxygenation in the sub papillary venous plexus and thus many factors other than the blood flow are involved That the effect of temperature of the blood is markedly shifting the dissociation curve (at 20 C blood is saturated by a PO of only 10 mm Hg) must not be forgotten Thus the intrinsic correlation with blood flow is very poor The reactive error is of course negligible

It is not generally known that the contrast between the skin colour of hyperæmia of ischæmia and of cyanosis can be greatly improved by the use of green light and of cross polarization of light (very simple nowadays with polaroid) This is shown in Fig 3 It was pointed out to me by Dr H K Hartline many years ago

Thermal Methods

Skin Temperature The interpretation of skin temperature measurements in terms of the peripheral circulation has been discussed elsewhere (Burton 1939) *The important starting*

point of critical analysis is to decide what it is that is measured i e the nature of the intrinsic variable This is the 'effective thermal conductivity (or its reciprocal the thermal resistance) of the whole thermal pathway from the core of the body where the temperature is constant to the point of measurement on the skin In many cases the major resistance to flow of heat may be in the last part of this thermal path way namely in the skin but the blood flow down the length

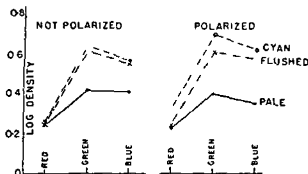


FIG 8 Differences in absorption of light of different colours upon reflection from the skin of the hand for different conditions namely Pale after immersion in cold water flushed after immersion in hot water cyan cyanotic after arterial occlusion at the wrist The increase in contrast is shown when the incident light is polarized at right angles to the plane of incidence and reflected light is received from a crossed analyser (From Publ No 13 Amer Assoc Adv Sci)

of the arm obviously also affects the skin temperature but in a predictable way By the use of a thermal circulation index based on sound physical theory this physical dependence of skin temperature can be eliminated and the effective thermal conductivity of the tissues deduced (Burton 1934)

As to the intrinsic correlation of the method of skin temperature the effective thermal conductivity must depend not only on the blood flow i e the 'convective' flow of heat but on actual conductivity in the stricter non convective

sense of the tissues (as in tissue without blood flow) The volume of blood or state of hydration of the tissues must also play a part As regards reactive errors these can be reduced to negligible amount by using fine enough thermocouples but many of the commercially available instruments for measuring skin temperature have a considerable reactive error since the heat loss of the area of skin where they are applied is seriously modified Only thermocouples of fine wire

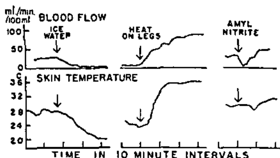


FIG 4 Simultaneous measurements of blood flow and skin temperature of a finger after various procedures The large thermal lag of the skin temperature is apparent and the inadequacy of skin temperature to indicate the time and the amount of changes in circulation that are transitory (From Publ No 13 Amer Assoc Adv Sci)

uncovered at the junction should be used Pressure of application can also give a considerable reactive error

The great disadvantage of skin temperature measurements is the large thermal lag involved so that where there is a brief though drastic change in the circulation skin temperature gives a most inadequate and wrongly timed indication of that change For changes in circulation that are relatively constant for several minutes however skin temperatures can give valuable indications of the peripheral circulation (Fig 4)

Local Thermal Conductivity The effective thermal conductivity of the skin can be more directly measured by several types of surface thermal stromuhr where heat is supplied

to the skin (it must be insufficient to elicit a reactive error) and the temperature rise in the steady state is measured when this heat is dissipated through the neighbouring skin I was able in the case of the fingers to correlate this measurement of effective thermal conductivity made in this way with the blood flow since in the finger the flow is almost exclusively to the skin The result is encouraging in that the intrinsic

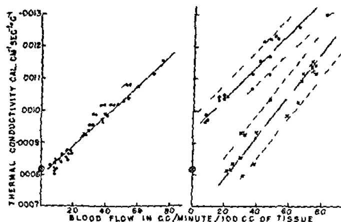


FIG 5 Effective thermal conductivity of the superficial 3 mm of the skin of the finger plotted against the simultaneously measured flow of the finger by venous occlusion plethysmograph The three sets of data are for three different subjects The points on the conductivity axis which are circled are for arterial occlusion of the finger when flow would be zero but the vessels congested The change in flow for other points were spontaneous or produced by heat or cold (Unpublished work of author)

correlation is excellent and the volume of blood trapped in the finger is relatively unimportant (Fig 5) Where the measurement is of the local conductivity (the depth under the skin to which the measurement is sensitive is easily determined) rather than as with skin temperature, of the whole thermal pathway the thermal lag is very small and such a device is sensitive to very rapid changes in the circulation of the skin

The Calorimetric Method

The method of Stewart has been used a great deal in recent years by Greenfield and his colleagues (1952) and by others The method using a vacuum flask is simple but has the inconvenience that if it is sensitive enough the temperature of the water soon rises above the desired range at which it was initially set By the use of the principle of the flow calorimeter i e measuring the difference of temperature between inflowing and outflowing water this can be avoided and the galvanometer readings give the rate of heat exchange directly We have succeeded in making such a calorimeter for the finger with a thermal lag when the heat of an artificial finger is turned on abruptly of only thirty seconds However there is an intrinsic lag in the method that cannot be removed in that whenever the blood flow to the finger changes the temperature of the tissues changes also Thus in the period of transition the heat exchange represents not merely that proportional to the blood flow but a large item from the thermal capacity of the fingers

The intrinsic variable of the calorimetric method is the calories/minute given up to the water If we knew the A V difference of temperature we could deduce the target variable in the flow in ml /minute While the assumption that the outflowing blood has reached the temperature of the water bath is reasonable though by no means accurate the assumption that the inflowing arterial blood is at deep body temperature may be very greatly in error (Bazett Love Newton Eisenberg Day and Forster 1948 Bazett Mendelson Love and Libet 1948) The method is useful therefore only as giving the minimal value for the blood flow i e we know it must be greater than that calculated on these assumptions There is also the difficulty as to the reactive error caused by vascular reaction to the temperature of the water It is difficult if not impossible to find a water temperature which will leave the finger blood flow what it would be in the normal environment of air However since the method has been used mostly to study the reactions of the finger to immersion in cold water

this is not a valid objection As with other methods improvement and practice in the methods of arterial and venous catheterization may enable us to use the calorimetric method in an unexceptional manner in which the A V difference of temperature would be measured simultaneously with the heat exchanges

Plethysmographic Methods

There is little need to point out how remote is the connection between changes of volume of a limb and changes in flow for this has been very generally realized The major portion of the volume in vascular beds resides on the venous side and because of the relatively great distensibility of the veins slight changes in venous pressure can produce large changes of volume On the other hand the arterioles chiefly control the flow and the volume of blood here is relatively small Thus the intrinsic correlation of volume measurements with flow is very poor However the same considerations have not generally been applied to the use of the volume pulsation with each heart beat which has been used as an index of peripheral blood flow We are convinced that most of the volume pulsation in a limb or digit originates in the capillaries and veins rather than in the arteries or arterioles Suggestive evidence for this statement is the remarkable dependence of the volume pulsation upon the distension of the venous vessels for a small rise of venous pressure will greatly reduce pulsation although flow is relatively unaffected Similarly under positive tissue pressure of a few mm of Hg which tends to empty the venous vessels the volume pulsation greatly increases in amplitude Thus although in conditions where the venous pressure is not altered there is an excellent correlation between finger volume pulsation and blood flow of the finger (Burton 1939) an alteration of venous pressure will greatly alter the slope of the line This is startlingly illustrated by experiments where the flow and the pulsation in the toe have been measured with different postures of the leg (Gaskell and Burton 1952) As the leg is raised

above the horizontal the flow reaches a maximum at a slight elevation above the horizontal and then declines with further elevation The volume pulsation however continues to increase in *amplitude to much greater elevations* This complicated relation of volume pulsation to flow is to be expected if the pulsation is mainly from the capillaries and venules for it will depend on the arterial pulse pressure the damping of this in the arterioles depending on their tone and finally on the distensibility of the venous vessels It is possible that the ingenious photo electric plethysmograph of Hertzman which has unique advantages in that it can be applied to any area of body surface measures something different from the plethysmographic volume pulsation of a digit It should be possible by incorporating in this apparatus selective filters such as are used in the oximeter to determine whether the pulsation which it records is from vessels containing venous or arterial blood

The Venous Occlusion Plethysmograph I had always felt that in the classical method of Stewart which has been so profitably employed by so many workers we had the method of choice for peripheral blood flow in an appendage It has withstood the critical evaluation of many workers There is no doubt that the intrinsic variable of the method is the target variable itself i e the blood flow in ml /min Thus the intrinsic correlation is perfect I am sorry to report that my confidence in the method has lately been shaken by the work of Dr Gaskell in our laboratory which reveals a reactive error in the method which we had not suspected The form of the curve of change of volume upon occlusion of the venous outflow is well known to all those who have used the method (Fig 6A) This is what we find when the measurement is made with the finger or toe at heart level But if the veins are distended either by lowering of the digit or by the raising of venous pressure by inflation of a distant cuff to a few mm of Hg pressure the curve becomes markedly different (Fig 6B) The initial slope supposed to give the rate of arterial inflow is much less than before and when the venous occlusion is

released the record of volume descends below the base line to rise later in an after dilation * When there is a high vaso motor tone so that the flow is reduced or if the digit is

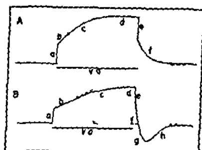


Fig 6 Schematic curves of volume change in a digit upon venous occlusion (V O) with th *superimposed cardiac pulsation* removed for sake of simplicity A normal with digit level with heart B with digit below heart or veins filled a cuff artifact b initial collection c diminished collection d steady state e reversed cuff artifact f emptying g after drop h recovery dilation

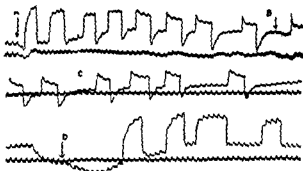


Fig 7 Plethysmographic flow records on the toe with the legs horizontal The subject sat up with legs horizontal at A and obvious signs of the venous reflex appeared At C he lay down but the records did not become normal until at D the leg was momentarily lifted to drain the veins (From *Circulation Research* 1 29 1953)

lowered still more we actually see the paradoxical result that upon venous occlusion the volume of the digit does nothing but decrease (Fig 7) We have discussed fully our interpretation of these curious results in the literature (Gaskell and

Burton 1952) The point here is that whatever the interpretation whether in terms of a myogenic reaction or a local reflex elicited by distension of the veins there is a decrease of volume of the blood vessels caused by the venous occlusion in the act of measurement Such a reactive error has been often considered but it was thought that it would take a few seconds to take effect upon the curve of volume and thus the initial slope would be unaffected This can no longer be maintained Even when there is no obvious sign of this reactive error (as normally with the digit at heart level) the artifact exists for raising the digit and emptying the veins usually results in an increased apparent flow Only when the veins are empty do we now have confidence in the absolute measurements of flow by this classical method

Conclusion

The result of such a critical approach to the available methods in terms of intrinsic variable intrinsic correlation and reactive error may seem depressing in that no methods are without criticism Yet as well as being good science such analysis yields dividends in revealing the factors other than the blood flow we wished to measure which may enter into each of the methods We are then in a position to make the best use of measurements made by many workers each with their own preferred techniques and by comparison of these results to learn more about the physiology of the peripheral circulation than any one of these workers set out to ascertain

In such a conference as this it is the differences in the results of different investigators that may lead to the greatest advances in our knowledge

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the apparent outflow was not due to slight movements of the wrist out of the plethysmograph

LYNN We occasionally encounter this phenomenon clinically when we try to measure blood flows in a limb with chronic venous insufficiency In deep venous thrombosis you occasionally cannot get a blood flow regardless of the collecting pressure you use You merely get a dropping off

DORNHORST It is a little misleading I think to say that the only thing which happens is shrinkage because the shrinkage is preceded by a sharp increase in volume which one gets from the artifact But some of that is probably a squirt of blood injected into the vessels and it is in fact accompanied by a sharp pulse of pressure in the vein It seems to be quite possible that some of this is just a wave produced in the already distended vein by blood running out and going back again

WHITNEY How long was the record continued after changing the position of the limb? Did you continue to get these reverse flows five minutes after?

BURTON There does not seem to be any real change in the picture you get with time

GASKELL I think we continued to get the same result as long as the limb was kept quite low It is not something which is going on continuously The vasoconstriction is at a certain level with the foot down and then when the cuff is inflated there is a further constriction and when the cuff is deflated it returns as a rule to its original level

WHITNEY But from a purely physical point of view it is rather peculiar isn t it? You are definitely preventing the blood which is coming into the arm from getting back to the heart and yet you are not getting an increase in size What do you suppose does happen? Where do you suppose the blood goes which is coming into the limb?

BURTON The only explanation for it is that the blood actually goes back up the artery There are plenty of animal experiments where we see this—when vessels close they do push blood back uphill One can also get away from all this consideration of artifacts due to blowing up a cuff one can show evidence of this kind of reflex from filling the veins simply by studying the change of volume in the digit when you change its level without any cuffs at all Any of you who have worked with the arm or hand know that when you raise it it shrinks permanently and when you lower it it increases in volume If you study the finger you discover that this is not so When you lower the finger the volume increases but the record immediately comes back again to the base line When the finger is raised the volume decreases but increases again These reflex constrictions and dilatations elicited by a change of level are easily seen on the records

A METHOD FOR RECORDING AND A STUDY OF THE VENOUS OCCLUSIVE TECHNIQUE FOR MEASURING THE TIME COURSE OF THE RATE OF INFLOW AND THE TIME COURSE OF THE RATE OF OUTFLOW IN THE FINGER TIP OF MAN DURING A SINGLE PULSE CYCLE*

G E BURCH

PLETHYSMOGRAPHY is one of the oldest procedures in physiological research It has been employed in the study of the circulation in visceral organs such as the spleen and kidney and portions of the extremities of animals The plethysmograph was first used to record only variations in volume of a part in association with variations in the circulation Brodie (1905) introduced the method of measuring the rate of blood flow in an organ by enclosing the organ such as the kidney in an oncometer and then obstructing venous flow from the kidney at its exit from the oncometer while recording the rate of swelling of the organ with time as blood accumulated therein From the tracing it was possible to measure the rate of blood flow into the organ Hewlett and Van Zwaluwenburg (1909) applied the same principle to the arm of man They enclosed the arm in a plethysmographic chamber and obstructed the venous outflow from the part enclosed within the chamber without apparent interference with the arterial inflow into the enclosed part The venous return was obstructed by inflating a Riva Rocci type of cuff applied on the arm proximal to the plethysmographic chamber to a pressure less than diastolic arterial blood pressure and above venous pressure The change in

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volume of the part with time as blood accumulated in the part was recorded by an apparatus connected to the pneumatic system enclosing the part From the record they calculated the rate of blood flow into the arm These procedures entail the fundamental principles of the venous occlusive plethysmographic method for measuring the rate of blood flow to a part

Although thermometric calorimetric direct bleeding and other methods exist for measurement of the rate of blood flow *this report is not concerned with these or with a review of the* subject rather it is limited entirely to the venous occlusive plethysmographic method for measurement of the rate of blood flow in the *finger tip* of man Most if not all of the principles described for the finger tip however apply to all applications of the venous occlusive plethysmographic method The finger tip is defined in this study as that portion of the finger located distal to a plane passing through and parallel with the major dorsal and palmar creases located in the vicinity of the distal interphalangeal articulation

This presentation is concerned with the description of a *method for measurement of the time course of the rate of inflow* into as well as the time course of the rate of *outflow* from the finger tip of man during a single pulse cycle It is a modification of a venous occlusive plethysmographic method developed by Turner (unpublished) A critique of venous occlusive plethysmographic methods in general the method described herein and methods of analysis of the data will be described in detail elsewhere It should be indicated however that most if not all methods (no exception could be found in the medical literature) involve measurement of the average rate of blood flow for one or more pulse cycles whereas the method reported herein is applicable to measurement of the average rate of blood flow as well as the time course of the rate of blood flow during a single pulse cycle Furthermore because many factors responsible for errors in recording have failed to be considered most previously existing methods and recordings have been subject to sig

nificant quantitative errors This is an attempt to improve the method for recording quantitatively the rate of blood flow through the finger tip

Materials and Methods

The normal young adult subjects rested in an air conditioned room (temperature 23 ± 1 C relative humidity less than 60 per cent) without perceptible draught This room is specially constructed to maintain equal air and wall temperature at all times and to minimize psychic disturbances (Neumann Cohn Burch 1942) Two types of sensitive plethysmographs were employed in these studies One has been described (Burch 1942) and the other was a specially constructed double recording sensitive plethysmograph The sensitive recorder of the latter unit consists of a rubber membrane suspending a small oscilloscopic mirror* (Burch to be published) This double recording plethysmograph permits simultaneous *recording of volume changes in two finger tips* The physical characteristics of performance of the two plethysmographs are essentially similar (Burch 1947) and are suitable for satisfactory recording of the rate of blood flow in the finger tip being sensitive to 0 1 cmm volume changes

The plethysmographic cup and occluding cuff applied to the finger tip in these experiments are shown in Fig 1 The occluding cuff was inflated and deflated by an automatically or manually controlled air pressure system Tubing led from an air reservoir with a pressure of 60 mm H_g experimentally determined to be a suitable pressure through a solenoid operated valve to the venous occluding cuff wrapped on the finger tip The solenoid valve was operated by an electronic switch (designed by Mr J A Cronvich) which was triggered by the pulse in the finger tip of the opposite hand and produced a signal by means of an electromagnetic microphone

*Westinghouse oscillograph vibrator supersensitive mirror No 59418? dimensions 1 × ½ × ⅛ mm

attached to the pad of the finger tip The circuit of the electronic switch was so designed that it was possible to produce sudden occlusion of venous return from the finger tip at any preselected point in the pulse cycle for any preselected period of time from less than 0 01 second which represents a small fraction of a pulse wave or pulse cycle to several pulse cycles Details of the circuit pneumatic pressure system and solenoid valve control will be discussed in detail elsewhere This method of venous occlusion made it possible to measure the rate of blood flow during part of

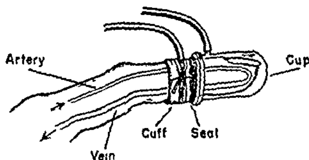


FIG 1 Diagram of plethysmographic cup and occluding cuff

the pulse wave and at a time when the "venous reservoir" * was not too distended with blood to permit accurate measurement of the rate of blood flow with minimal disturbance in hæmodynamics or blood flow in the finger tip

The venous occluding cuff was placed directly against the plethysmographic cup and the sealing material so as to produce obstruction of venous outflow as close as possible to the plethysmographic cup enclosing the finger tip (Fig 1) Thus the blood flowing into the finger tip from the arterial system

*The "venous reservoir" as used in this report included primarily the large veins but blood most likely accumulates during the later period of measurement in vessels closer to the arterial side such as venules capillaries and anastomotic vessels Initially the blood must accumulate in the large veins of the finger tip The precise anatomical nature of the venous reservoir is unknown

accumulated in the venous reservoir enclosed within the plethysmographic cup where it could be recorded and not as is so often done in studies of this type in veins outside the plethysmographic cup where it cannot be measured (Abramson 1941 42 Goetz 1948) When the cuff occluding the venous return was inflated an artifact was produced in the record of the volume change This artifact is a volume time course curve and appears in the tracing as part of the curve of the volume time course of blood flow A method of analysis was developed to subtract this artifact volume time trace from the volume time trace recorded during the measurement of blood flow (Burch to be published) this method is briefly summarized by Figs 2 3 and 4 It has been found experimentally that this artifact is reproducible for given conditions of measurement of the rate of blood flow Whenever changes were made in the conditions a volume time course of the artifact for the new conditions was determined The artifact curve was determined by first suddenly arresting the circulation to the hand by means of an ordinary arterial blood pressure cuff applied to the brachium and then after the circulation has been arrested inflating the venous occluding cuff at the site of the plethysmographic cup on the finger The recording volume change with time produced by inflation of the occluding cuff on the finger constitutes the artifact curve of the volume time course (Fig 3)

The subjects were permitted to rest comfortably in a hospital type bed in the air conditioned observation room Their clothing fitted loosely and did not interfere with blood flow to the part The arm rested on a special arm rest (Burch 1947) with the finger tip at the level of the heart Plethysmographic recordings of the volume pulse wave for the third right finger tip were made on photographic paper simultaneously with recordings of the rate of blood flow into and out of the second right finger tip This made it possible to relate any selected portion of the completed curve of the time course of the rate of blood flow in the second right finger tip with any phase of the peripheral volume pulse wave or the

pulse cycle in the finger tip It appears unlikely that the pulse waves in two adjacent finger tips would be sufficiently different to invalidate significantly any correlations of the two simultaneously recorded traces

The Plethysmogram

1 *The time course of the volume and the time course of the rate of blood flow into the finger tip* —A typical plethysmogram as actually recorded with a normal subject at rest is shown in Fig 2 The first part of the recording shows the pulse and alpha waves (Burch Cohn Neumann 1942) simultaneously recorded for the second and third right finger tips at slow camera speed The speed of the camera was then increased and after one or more pulse waves had been recorded the occluding cuff on the second right finger tip was suddenly inflated This resulted in a curve of the volume time course (Fig 2) which reflected the volume change produced by the artifact as well as the accumulation of blood in the venous reservoirs within the plethysmographic cup distal to the venous occluding cuff

It is possible to subtract the volume time curve of the artifact (Fig 3) from the volume flow curve shown in Fig 2 to obtain the time course of the volume of blood flow into the finger tip during a pulse cycle This is also a curve of energy due to the blood flowing into the finger tip

Fig 4 summarizes the method by which the trace of the time course of the rate of blood flow into the finger tip was obtained The volume time curve of the artifact was placed under the volume time curve of blood flow the point in time at which the occluding cuff was inflated being superimposed by means of tracing paper with the proper abscissa of time being maintained Then the volume time curve of the artifact was used as the baseline to determine the volume change in blood in the finger tip with time A derivation of the blood volume time course was obtained by plotting the difference in volume with time at each 0 02 to 0 04 second The resultant curve (Figs 4 5) represented the time course of the rate

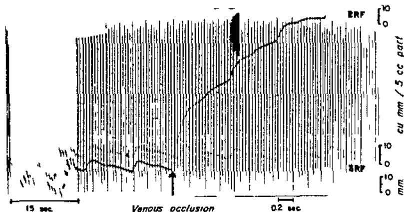


FIG   Actual plethysmogram   Arrow indicates moment of inflation of occluding cuff on second right finger (2RF)   The resultant change in the trace for the second right finger at this point   due to accumulation of blood within the plethysmographic cuff   Simultaneous recording of the third right finger (3RF) is shown   The magnitude of deflections in mm and in cu mm per 5 cc of part can be determined from the scales to the right of the illustration   The pulsations in the initial portion of the plethysmogram were recorded at slow camera speed and the remaining portion at fast camera speed

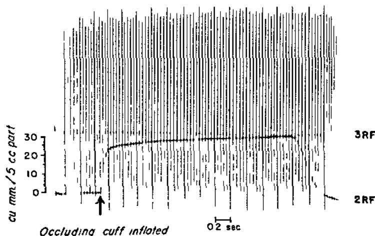


FIG 3   The time course of volume produced by inflating the occluding cuff with circulation to the fingers arrested

of blood flow *into* the finger tip This is also a power curve Necessary corrections were made to reduce the completed trace to a time course curve of the rate of blood flow in units of cmm per 5 c c of part per second (Burch 1947) For comparison of these rates of blood flow with those reported by others this unit may be changed to c c per 100 c c of

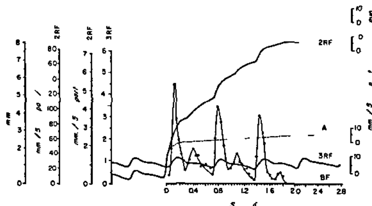


FIG 4 The rate of blood flow was calculated from the plethysmogram as follows The artifact volume curve A was subtracted from the volume curve of the second right finger (2RF) following inflation of the occluding cuff The resultant change in volume represented the volume of blood accumulated with time due to the arterial inflow The change in volume at 04 second intervals was then obtained and converted to rate of blood flow in cu mm per 5 cc part per second These values were plotted on an ordinate system magnified two and one half times in order to show details The scales for this magnified ordinate system are shown to the left of the illustration The actual magnitudes of the plethysmogram are shown to the right of the illustration The time course of the rate of blood flow curve (BF) is also shown

part per minute by multiplying the values by 1 2 A typical curve of the variations in the rate of blood flow into the finger tip of a normal subject at rest during a pulse cycle is readily evident from Fig 5 The simultaneous recording of a volume pulse wave of the third right finger tip is shown which permits relating the rate of blood flow to various phases of the pulse cycle

2 *The time course of difference between the rate of blood flow into and out of the finger tip*—The volume pulse wave recorded plethysmographically is the volume time curve of the change in blood volume in the finger tip produced by difference in volume inflow and volume outflow of blood with time during a pulse cycle (Fig 6) This is an energy curve An

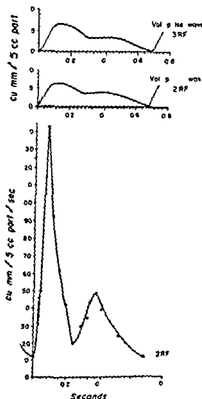


FIG 5 Typical curve of the time course of the rate of inflow for the second right finger (2RF) of a normal resting subject during one pulse cycle The pulse waves shown at the top of the illustration for the third right finger (3RF) was obtained simultaneously with the measurement of flow for the second right finger The pulse wave shown for the 2RF was the one recorded immediately before inflating the occluding cuff for the measurement of blood flow

ascending deflection occurs when volume inflow exceeds volume outflow with time and a descending deflection occurs when volume outflow exceeds volume inflow with time (Fig 6) The time course curve of the first derivative of the volume pulse wave is a rate curve (Fig 7) This is also a power curve It represents the time course of the difference between the rates of flow of blood *into* and *out of* the finger tip with time Details of the variations of this curve during various phases of the pulse wave can be obtained from a study of Fig 7

3 *The time course of the rate of blood flow out of the finger tip* —It is possible to determine the rate of outflow of blood

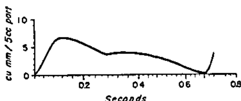


FIG 6 This is a typical volume pulse wave for 2RF for a normal subject at rest

from the finger tip by subtracting the time course curve of the difference between the rates of inflow and of outflow from the time course curve of the rate of inflow to the finger tip That this procedure is valid is evident from the equations

$$I-O=D \qquad (1)$$

$$\text{or } O=I-D \qquad (2)$$

where I=rate of blood flow *into* the finger tip O=rate of blood flow *out of* the finger tip and D=difference between the rates of inflow and outflow

Fig 8 shows the time course of the rate of *outflow* from the finger tip obtained by subtracting the time course of the first derivative of the volume pulse wave in Fig 7 from that of the rate of inflow in Fig 5 The volume pulse wave of the

third right finger tip recorded simultaneously with the rate of blood flow into the second right finger tip was used to obtain the rate of outflow for the second finger tip Because the two fingers were different and therefore, there could result an erroneously calculated record of the rate of outflow for the

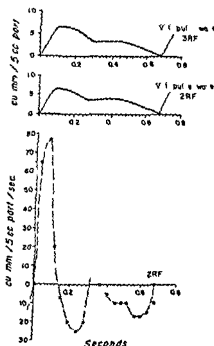


Fig 7 Time course of difference between the rates of inflow and outflow

second right finger tip the rate of outflow was also calculated by use of the volume pulse wave for the second right finger tip which occurred just preceding inflation of the occluding cuff The resultant calculated curves of the time course of the rate of outflow of blood for the second right finger tip differed only slightly No attempt has been made as yet to determine whether or not the slightest differences are significant The rate curves shown in this paper were all plotted

from calculations made from the volume pulse wave of the second right finger tip which just preceded inflation of the occluding cuff A study of Fig 8 reveals the variations in the rate of outflow at various phases of the pulse cycle It is

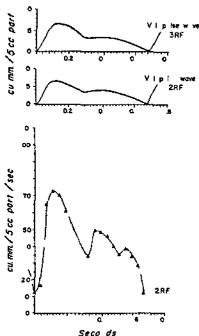


FIG 8 Time course of rate of outflow of blood for the same pulse cycle shown in Figures 5 and 7

evident that the rate of venous outflow from the finger tip is pulsatile and not a steady continuous rate of flow

Fig 9 shows the three different time course curves of the rates of blood flow for the finger tip It is evident from this illustration that the major deflections of the rate curve for outflow are shifted to the right in time with respect to the in flow curve For example when the rate of inflow increases rapidly at the onset of the pulse cycle the outflow rate is

relatively low and still declining About 0 03 seconds later the outflow curve rises rapidly It is evident also that at least four times during the pulse cycle the two curves cross At those points in time the difference in the rates of inflow and

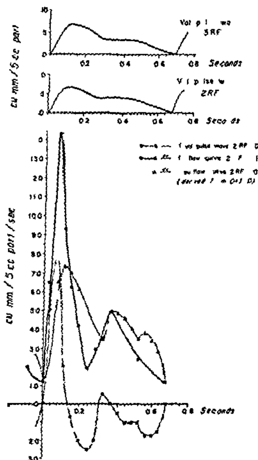


FIG 9 Composite drawing of the curves of the rates of inflow outflow and difference between rates of inflow and outflow for the second right finger (2RF) in a normal resting subject for the same pulse cycles shown in Figures 7 and 8 This illustration permits correlation of phase and quantity relationships between the respective curves and the volume pulse wave

outflow is zero There are other interesting characteristics in relationships among the three curves which become evident with careful study of them It is also possible to obtain simultaneous plots from the plethysmograms of the time

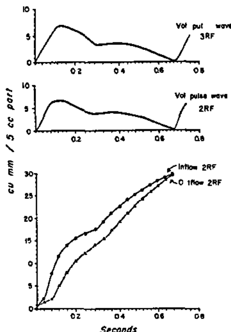


FIG 10 Time course of volume inflow and outflow obtained for the same pulse cycle for the second right finger of a normal resting subject

course of the volume flow *into* the time course of the volume flow *out of* and the time course of the *difference* between the volume flow into and out of the finger tip (the volume pulse wave)—Fig 10 The volume changes are expressed in units of cmm /5 c c of part The volume pulse wave of the third right finger tip was recorded simultaneously with the volume inflow and outflow for the second right finger tip to permit

detailed correlations of volume changes in the second right finger tip with the phases of the pulse cycle

Discussion

The method of recording the rate of blood flow in the finger tip described in this report is relatively simple It is theoretically accurate but its accuracy cannot be determined directly at the present time Although the method appears to be relatively accurate certain factors which may produce errors in measurement require constant consideration These factors will be discussed more completely in a future report Regardless of the possible errors and variables yet to be completely evaluated for the method the technique offers many advantages and possible applications in the study of the circulation to the finger tip By this method it is possible to study not merely mean rates but detailed variations with time for single pulse cycles in volume inflow and outflow and in the rates of inflow and outflow as well The mean rates are easily calculated from the curve of course by determining the total change in volume per pulse cycle of measured duration The same principles employed herein in the case of the finger tip for measurement of the time course of volume inflow and outflow the rate of inflow and outflow for a single pulse cycle and the mean rate of flow per cycle can be applied to larger parts such as the hand foot, limbs or segments thereof

The fact that it is possible to record the time course curves of the rate of inflow and the difference between the rates of inflow and outflow for the finger tip and to calculate the time course curves of the rate of outflow makes it possible to study many important pulsatile phenomena and other hæmodynamic phenomena for the finger tip of man in normal and disease states For example additional aspects of the problems concerning variations in configuration of the pulse wave of the finger tip can now be studied for man for many different normal and vascular disease states It should be possible to differentiate vascular phenomena which originate primarily in the arterial side of the circulation from those which are

primarily in the venous side Observations of these types are now in progress in this laboratory

Gregg and his associates (Shipley Gregg and Schroeder 1943 Gregg 1950) studied curves of the rate of blood flow in arteries of the dog and recorded simultaneously pressure and arterial blood flow by means of the orifice flow meter They calculated volume elastic flow curves by assuming that venous outflow of blood from the part changed little during a pulse cycle This assumption was supported by direct measurement Therefore if the rate of venous outflow of blood from the part is represented by a horizontal line or is of constant rate then from the arterial flow curve venous outflow curve and pressure curve they constructed a volume elastic flow curve (V E flow curve) The V E flow curve so constructed appears to be the same as the volume pulse wave recorded plethysmographically for the finger tip Unfortunately Gregg and his associates did not attempt to record a volume pulse wave or V E flow curve plethysmographically to check their calculations Such a plethysmographically recorded volume time curve would have thrown light on the relationship of the V E flow curve and the volume pulse wave recorded for the finger tip The same principles relating to viscous resistance to flow and inertia which they applied to their tracings for large arteries and large parts such as limbs or parts thereof can be applied by the method of study described in this report to the intact finger tip of man with relatively little disturbance to the subject or circulation The papers of Gregg and his associates should be consulted for details concerning these problems

It is interesting that Gregg and his associates found no significant variations in the rate of venous blood flow in large veins of dogs during the pulse cycle whereas the observations obtained in these studies revealed large pulsations in the rate of venous flow from the finger tip of man That venous flow is relatively constant during the pulse cycle as reported by Gregg is probably due to the smoothing out of the rate of venous flow by the many circulatory circuits of venous

lengths, each of which contributes independently and at different times during the pulse cycle to the return flow of venous blood from a longer and larger part such as the limb All joining tributaries may empty blood with a pulsatile flow but since the magnitude and time of the various pulsations are variable the resultant rate of flow is reduced to a smooth and relatively constant rate In the case of the finger tip the circuits are not as numerous the lengths of the veins returning blood to the heart are short and essentially equal in length and are located near the terminus of the arterial side of the peripheral circulation Under such circumstances the pulsatile rate of blood flow found in the arterial system of the finger tip would be expected to be transmitted directly to the venous system It would appear that the farther the vein is from the periphery until the chest and heart are closely approached the less would be the pulsation in the rate of venous blood flow and the more peripherally located the vein the more pulsatile would be the rate of blood flow It is evident from these experiments that the veins of the finger tip pulsate with the heart beat as does the arterial side of the circulation *If the arterial and venous vessels pulsate then those between* such as the capillaries and A V shunts must also pulsate with the heart beat

Gregg and his associates (Shipley Gregg and Schroeder 1943 Gregg 1950) as well as others (Hewlett and Von Zwaluwenburg 1907) occasionally noted backward flow in large arteries such as the femoral axillary or carotid arteries Such backward flow has not been definitely observed so far in these studies on the finger tip of man either normal or diseased The significance of these differences between the larger vessels of the extremities and the finger tip remains to be clarified It is possible that the more peripheral the artery is the smoother the rate of blood flow would be and the less likely would be the opportunity for backward flow " whereas the more centrally located the artery is the more likely would it be for this to occur In the presence of a competent aortic valve it is difficult to visualize where the backward flowing

blood would go It is possible that a portion of the blood which flows backward in the large central arteries perfuses the myocardium by way of the coronary vessels The influence of technical errors and the effects of the distension of the large central arteries upon the recordings made by orifice flow technique must be understood before backward flow can be fully accepted Arterial backward flow in the heart probably takes place to a measurable extent from the large central arteries in subjects with aortic valvular incompetence even though it has not been possible so far to demonstrate definitely backward flow in the finger tip of such patients This may occur for the finger tip under certain circumstances of aortic valvular regurgitation and of the peripheral circulation however

The total area enclosed by the positive portions of the time course curves of the difference between the rates of inflow and outflow should equal the total areas enclosed by the negative portions during a steady state or state of vascular equilibrium for the finger tip This should be true because the net inflow should equal the net outflow for a pulse cycle Should there be vasodilatation with increase in volume of the vascular bed of the finger tip the rate of inflow would exceed the rate of outflow during the pulse cycles occurring during the period of vasodilatation Under such circumstances the total area enclosed by the positive deflections would exceed the total area enclosed by the negative deflections of the curve of the time course of the differences in the rate of inflow and outflow On the other hand during a period of vasoconstriction or reduction in volume of the vascular bed of the finger tip the rate difference curves should manifest a larger total area for the negative deflections than for the positive ones

With vasodilatation or vasoconstriction there is a shift in time of all or portions of the inflow and/or outflow curves due to necessary changes in the time course of the rate of blood flow in either or both inflow and outflow depending upon the physiological circumstances For example if vasodilatation of the vascular bed of the finger tip occurs with accumulation

of blood within the finger tip due only to dilatation of the capillaries venules and other vessels distal to the arterioles and occurs in such a manner that the A V pressure gradient is essentially unaltered the time course curve of inflow will remain essentially unchanged in its configuration magnitude and time course during the period of vasodilatation The time course curve of outflow will be reduced in magnitude with shifting of at least the terminal deflections to the right of the others within the composite plot of the rate of flow curves of the type shown in Fig 9 During the period of constriction of the vessels distal to the arterioles with insignificant change in the A V pressure gradient the time course curve of the rate of inflow would be expected to change little if at all detect ably whereas the time course curve of the rate of outflow would increase in magnitude with a possible tendency for it to shift to the left of the composite plot of the flow curves as shown in Fig 9 It is possible for certain portions of the time course curves of the rate of blood flow to change more than other portions Details of the variations for various normal and abnormal physiological states must be determined by experimentation Changes in the rate of narrowing or en larging of the vascular bed distal to the arterioles will alter the configuration of the time course curves of the rate of outflow accordingly Obviously once vasoconstriction or vasodilatation of the vascular bed has occurred and a new steady state has been established for a new volume of the vascular bed the configuration of the time course curve of outflow will tend to resemble the inflow curve in a relation *ship characteristic for the steady state found in association* with the new hæmodynamic state

On the other hand if the vasoconstriction or vasodilatation should occur only for the arterioles and arteries the time course curve of the rate of inflow would be primarily altered during the vascular changes Since under these circumstances the rate of inflow determines the rate of outflow the time course curve of the rate of outflow will tend to change in a similar fashion depending upon the inflow curve Arteriolar

vasoconstriction or vasodilatation will involve primarily a decrease or an increase in the magnitude of the rate of flow curves Obviously the changes in configuration of these flow curves and their respective temporal relationships become even more complex to visualize when the arterial capillary and venous portions of the circulation are constricting and dilating independently at either or both different times and rates Changes in the configuration of the various rate curves require further study for these various vascular physiological conditions

The curves of the time course of the rates of blood flow (*inflow outflow or difference between these two*) *drawn in* these experiments are probably in error in regard to the details For example instead of connecting the points plotted at 0 02 second intervals smooth curves were drawn among them by inspection This was done to simplify calculations in view of the human errors inherent in analyses of this type Under the method of analysis employed in these studies the time course curves of the rates of blood inflow and outflow were characterized by two main positive waves a large systolic wave (systolic positive wave) which occurred during the systolic period of the pulse cycle and a smaller wave (diastolic positive wave) which occurred during the diastolic phase of the pulse cycle just after the dicrotic notch (Figs 5 and 8) A more careful analysis of many curves should clarify the significance of the many small waves in the curves

Summary

A method has been described for measurement of the time course of the rate of blood flow *into* and *out of* the finger tip of man during a single pulse cycle The physiological importance of the study of the configurations and magnitude and temporal relationships of the time course curves of the rates of inflow outflow and the difference between these in the understanding of hæmodynamic phenomena in the peripheral circulation of normal and abnormal physiological vascular states has been briefly indicated

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TURNER R H Unpublished studies

DISCUSSION

HERTZMAN One question which I would like to raise is the relationship of the width of the occluding cuff to whatever happens in the plethysmograph In making measurements of digital arterial pressures I found that a cuff narrower than 20 mm of Hg simply would not give correct values—it gives too high values for systolic blood pressure Now we are dealing with a very high velocity of blood flow in the digital veins The occluding cuff may have to be quite wide in order to overcome momentum Is the venous occlusion technique modified by the rate of flow in relationship to cuff width? This is a purely theoretical consideration but I wonder if it has been examined systematically?

BURCH We have tried cuffs of various widths and decided to employ one about 6 mm in width Difficulty is apt to occur if the cuff is too narrow or so wide as to overlap slightly flexed joints The cuff should transmit the pressure evenly

We have not worked very much with the toe primarily because of its short length and difficulty with the application of the occluding cuff It may be added that the pressure employed in the inflation of the cuff probably should vary as the subject s blood pressure varies to obtain constant conditions

HERTZMAN How does the technique work out when the digital artery is partially occluded by disease or by compression with a resultant decrease in the digital arterial pressure?

BURCH We have not studied that but there must be some interference with blood inflow To assume that when a cuff is placed around a finger inflation of that cuff causes obstruction only of venous outflow is erroneous because near the surface of the finger are small vessels branching from arteries slightly proximal to the plethysmographic cup

which are probably obstructed when the occluding cuff is inflated This must reduce arterial inflow to some extent

HERTZMAN I have been very sceptical about the use of correlation coefficients in this field Our need of course is to have some absolute yardstick But still if with the high levels of flow recorded by the venous occlusion technique you get values fairly close to calorimetric measurements it might be worthwhile to plot the relation There won t be absolute proof though

BURCH I do not intend to defend strongly the correlation coefficients presented Their value is self evident To know a rate of flow for any given moment of conditions one must actually measure the rate It cannot be obtained from a correlation coefficient or regression curve

SHEPHERD Dr Patterson and I have been doing some experiments on the forearm blood flow in which we have temporarily increased the volume of blood in the forearm by inflating a cuff around the arm to about diastolic pressure for five minutes On release of the pressure there is a transient decrease in forearm flow followed by an increase to the resting level prior to the application of the cuff We do not yet know the mechanism of this response but it may be relevant to Dr Burton s earlier remarks

EDHOLM Can you detect any venous reactive hyperæmia?

SHEPHERD The first flow which is recorded about two to five seconds after release of the pressure is fairly high the flows recorded over the next minute or so are less than the resting level The flow then returns to the resting value

EDHOLM Dr Werner has been studying similar problems—did your finding agree with these?

WERNER No not quite In our experiments there was an increase in flow for fifteen to thirty seconds after occlusion at 80 mm of Hg then a decrease in flow and finally a return to the control flow However the mean of these changes in flow following venous occlusion was no greater than the control blood flow

BURCH I have noted illustrations of actual recordings of flow measurements in the literature and most of them if not all show negative deflection regressions in the traces during intervals of time when the rate of flow was measured There can be no decline in the trace unless there is backward flow or leakage past the occluding cuff I have never found backward flow in the arteries of the finger tip It has been recorded for large and more centrally located arteries I cannot doubt these findings but I warn of the possibilities of instrument errors which suggest backward flow Every severed artery that I have seen did not suggest backward flow but such an artery is without its peripheral vessels When the method permits measurement of blood flow for a fraction of a pulse beat negative flow can be evaluated better It probably is due to error in most instances

DAWES I am not sure that I understand that surely a reverse flow could occur down the arteries?

BURCH I suppose it is possible for large centrally located arteries in normal man and dog although I would like to see backward flow more

definitely established and studied It is my opinion that technical errors are responsible for the negative deflections shown in the plethysmographic recordings of blood flow and not reversal of blood flow

LUNDHOLM Dr Macdonald has demonstrated reverse flow in the aorta in rabbits using high speed photography of the movement of dye and bubbles Reversed flow also occurs in the iliac and femoral arteries

BURCH Where is the blood going during reversal of flow in the arteries?

DAWES It's going back up the aorta isn't it?

BARCROFT One of the places it could go through would be the coronary and intercostal vessels

BURCH Yes I am sure that is true but the quantity must be small and the blood must originate from the aorta near its origin from the heart

DORNHORST I think reverse flow can happen in the brachial artery under some conditions if you are measuring pressure in say the radial artery and you suddenly occlude the arteries above you may find that it will settle down to a pressure considerably above the diastolic I think that must mean that during diastole the blood is running back

BURTON Mr Chairman we need to be very careful about the choice of words Dr Burch was talking about negative flows I think what he meant was negative deflections which we mistake in calling negative flows I think there definitely are negative flows which can be seen by direct observations In our animal experiments where the artery is occluded flow stops at a certain pressure which we call the critical closing pressure When the pressure in the artery is then artificially lowered below this it actively rises to the original level I think it would be better to use the word shrinkage It is dV/dt which is negative i e it is a shrinkage of volume and this does not necessarily imply a negative flow in the other sense It means that at that moment the outflow is exceeding the inflow and this is the way Dr Burch has been using it

BURCH I think the negative deflections in the plethysmogram are evidence of leakage through the incompletely occluded veins

BURTON I should emphasize that there is very definite evidence in this critical closure we talk about that blood does flow back uphill It flows back into the arteries which is a true negative flow rather than just a shrinkage

THE ELECTRICAL STRAIN GAUGE METHOD FOR MEASUREMENT OF PERIPHERAL CIRCULATION IN MAN

R J WHITNEY

Introduction

THE method which I shall describe depends on a technique the mercury in rubber strain gauge of which I gave a pre liminary account some three years ago (Whitney 1949) Since that time this technique has been adapted for recording changes in the limb volume of man and the apparatus has been given considerable use in examining responses of the peripheral circulation which are accompanied or which may be accom panied by changes in limb volume In short the apparatus has been used instead of the conventional air or water plethy smograph Since I now have in the press (Whitney 1953) a fairly extensive account of the pros and cons of the gauge method for studying peripheral circulation I propose to restrict myself so far as an account of the method is con cerned to those aspects of it which seem to require discussion and clarification I greatly value this opportunity of des scribing my method to an audience which is so highly qualified to judge its merits or demerits

Since some of you may not be aware of the gauge method in its present form a brief description of this will not I hope be out of place First of all however I should like to mention why I found it necessary to find an alternative to the con ventional plethysmograph for recording limb volume changes in man

Leaving aside many criticisms of the plethysmographic technique some of which criticisms have been rendered less real in recent years by members of this audience I shall confine myself to mentioning those deficiencies of the tech nique which seem insuperable —

1 With the air or water plethysmograph, the portion of the limb under investigation has to be "shaded" from the ambient conditions to which the rest of the body is exposed

2 For records of limb volume changes over a considerable period with possible variations of air and skin temperature it is necessary to control thermostatically the temperature of the fluid filling the plethysmograph

3 The conditions under which the plethysmograph can be used are unduly limited with regard to position of the apparatus on the body and with regard to the posture and activity allowed to the subject It is usually necessary to impose some measure of restraint on the subject which may conceivably affect the nature of the circulatory response for which the plethysmograph is being used

The Gauge Method

Faced with the problem of recording limb volume changes and peripheral blood flows of a man subjected to alternating periods of work on a bicycle ergometer and rest under hot room conditions I decided that some alternative would have to be found to the method of recording volume change directly with the plethysmograph I concluded that it should be possible to obtain such a record by actually measuring changes in limb girth with the mercury in rubber strain gauge and by deducing the required volume changes from these measurements The arguments both theoretical and practical, for this conclusion I have set forth fully in the paper already mentioned (Whitney 1953) and I shall proceed to a brief description of the apparatus and its method of use

Fig 1 shows the gauge mounted on a limb with the subject in a natural posture This emphasizes the ease with which the gauge can be mounted without imposing undue restraint on the subject Details of the construction of the gauge of the system of thermal compensation and of the procedure for its use have been fully described (Whitney, 1953) and need not be repeated here Fig 2 shows the practical lay out of the apparatus for recording changes in the forearm Calibration

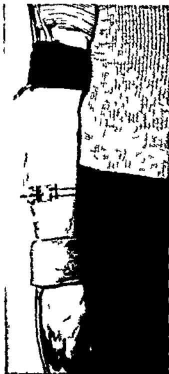


Fig 1   Gauge mounted on ri,_ht forearm with wri t and ui per arm occlus on c iff   Note strips of adl ive tape to prevent gauge sli pin,_ d)wn tl e arm di ring movement

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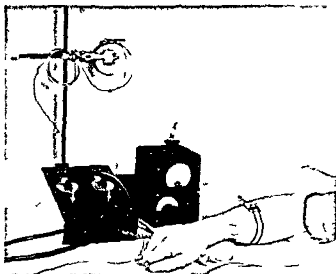


FIG 2 Apparatus used with strain gauge The box on the left contains the bridge circuits for two gauges together with switches for the galvanometers the recording camera motor and the power supply to the bridges The bridge box has long lead connections (bottom left hand corner) to the recording galvanometer and a short lead connection to the power supply box (right) which contains the batteries and the metered voltage dropping circuit One gauge is shown mounted on the forearm the other being mounted on the circular wooden former on which it is kept when not in use

on the limb is usually carried out by screwing up the adjusting screw a definite number of turns (usually 4) and noting the deflection of the baseline The percentage girth change equivalent to 1 mm deflection of the record is then obtained by dividing 100 by the product of the limb girth (in mm) and the mm deflection of baseline produced during calibration per 1 mm alteration in the adjusting screw The percentage volume change equivalent to 1 mm deflection of the record will be twice the corresponding percentage girth change, for reasons given fully in my recent paper (Whitney 1953) All these calculations and the direct reading of peripheral blood flow if the gauge is used in conjunction with the venous occlusion technique are readily carried out by a suitably designed nomogram and bevel board

In comparing the gauge method with the usual plethysmographic one it will be seen that many of the undesirable features of the latter are more or less overcome The gauge is easy and quick to mount on the subject a negligible part of the limb is shaded from surrounding conditions the record is thermally compensated the subject can assume normal postures and can be allowed a large measure of freedom without dismounting the gauge and without risk of displacing the gauge from its position on the limb If very free activity is allowed it has been found quite adequate to ensure positive location of the gauge on the limb to bridge the gauge mounting and its strands with narrow strips of adhesive plaster In addition it will be noted that the calibration of the gauge is a live one simulating a known change of limb girth unlike calibration of the plethysmograph which is essentially a calibration of the volume recorder only The somewhat messy and rather inaccurate measurement of the volume of the limb enclosed in the plethysmograph is replaced by the rapid and comparatively accurate measurement of limb girth

I think that I can largely leave to your discussion of this paper the question of the reliability of the gauge record of limb volume change I shall only say here that the principle

on which the gauge method depends can be and has been submitted to quite exhaustive theoretical and physical checks The principle of the plethysmograph has not to my knowledge been submitted to such treatment It might be thought that the two strand gauge samples too short a segment of the limb compared with the plethysmograph Actually such restriction of the sample is not inherent to the gauge method for separate two strand gauges can be mounted at intervals

Table I

HUMAN FOREARM BLOODFLOW ARM FULLY IMMERSED IN WATER AT 35 C (44 RECORDS ON FIVE SUBJECTS)

	Mean flow cc/per min	SE Mean	SD Flow	Actual range of flow
Proximal gauge	3 40	0 23	1 53	1 82 – 7 70
Middle gauge	3 32	0 19	1 25	1 69 – 7 01
Distal gauge	3 19	0 14	0 94	1 82 – 5 08
Combined gauge	3 50	0 17	1 13	1 94 6 40
Plethysmograph (Barcroft and Edholm 1943)	4 00			1 5 – 7 0

along the limb or a single multi strand gauge can be used to record from a larger segment Actually such expedients are not always necessary as results from the use of several two strand gauges on the forearm indicate (Table I) It might also be claimed that the gauge cannot be used to record volume changes in a whole terminal part such as a hand or foot This is substantially true but mention will be made later of a possible method of deducing hand or foot blood flows from gauge measurements made on the forearm only It will be admitted that such expedients if justifiable are highly desirable for the exclusion of the hand or foot from the

ambient environment necessary with the hand or foot plethysmograph is thereby avoided

I will conclude with a rapid survey of some of the results which have been obtained with the gauge method In some

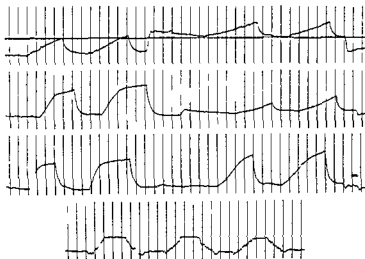


FIG 3 Typical venous collection curves (upper three rows) and a calibration record obtained with the gauge mounted on the forearm Time mark 4 secs Each row of curves shows two records without arterial occlusion of the wrist followed by a record of the application of wrist occlusion followed by two collection curves with the wrist occlusion maintained

of these I would like you to consider if the usual plethysmograph could have been used instead of the gauge

Fig 3 shows typical venous collection curves recorded from the forearm of the resting subject with and without the application of arterial wrist occlusion The sigmoid curves which are typically obtained with the gauge when the wrist is occluded are shown I believe that this indicates the possibility of a control of peripheral blood flow by the pressure

of blood in the veins From this type of record, hand flow is deduced according to the formula

$$F_H = \frac{V_A}{V_H}(F_1 - F_2) + F_1$$

F_H	=	Hand Bloodflow (cc /100cc tissue/min)
F_1 F_2	=	Initial rate of swelling of forearm during venous collection without arterial occlusion at wrist (F_1) and with such occlusion (F_2) cc /100cc tissue/min.)
V_A	=	Volume of forearm
V_H	=	Volume of hand

and hand flows so deduced are in general agreement with those recorded with the hand plethysmograph under approximately the same conditions

Fig 4 gives the records obtained when estimating the effect of venous hydrostatic pressure on venous distensibility of the

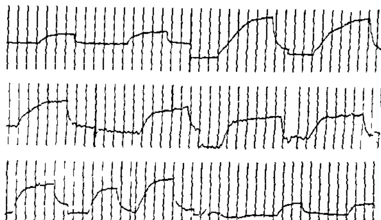


FIG 4 Venous collection curves obtained from the forearm of a subject on a bicycle ergometer Reading from top left to bottom right 1 and 2 at rest with hands lowered onto handle bars 3 and 4 at rest immediately after arm raised to horizontal rest 5 to 8 obtained at intervals during twenty minutes of pedalling the arm remaining horizontal 9 to 11 during resting after work arm still horizontal 12 and 13 immediately after returning hands to handlebars

forearm The distensibility is estimated from the height of the shallow part of the venous collection curve above the baseline when a uniform collection pressure (50 mm Hg) is used The subject was on a bicycle ergometer and it will be noted that an increase of distensibility accompanies a lifting

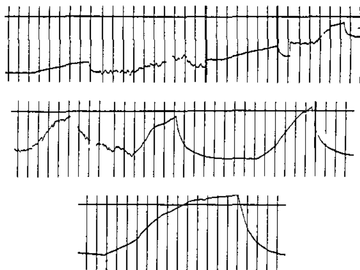


Fig 5 Venous collection curves from forearm of subject on bicycle ergometer Reading from top left to bottom right 1 resting arm hanging by side during and after ten minutes of pedalling 3 at rest after thirteen minutes pedalling 4 during resumed pedalling 5 during pedalling (after thirty three minutes work in all) and two minutes after raising arm from side to a horizontal rest 6 to 8 successive records during rest after work arm remaining on horizontal rest

of the hands from the handlebars so that the forearms assume the horizontal The distensibility is reduced during work but increases again as soon as work ceases Distensibility can be immediately reduced by lowering the hands on the handlebars These records show what type of record is obtained from an inactive part during actual work (pedalling)

Fig 5 indicates a similar effect of change of posture on the distensibility of the venous system The arm was moved from the hanging to the horizontal position during pedalling *after the fourth collection curve in the Figure The almost* immediate increase in distensibility during work and its

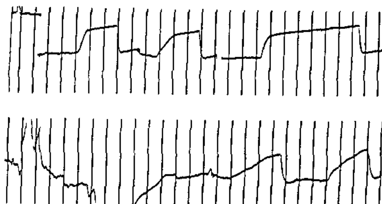


FIG 6 Venous collection curves from the forearm of a subject resting, *after stepping exercise successive records reading from* top left to bottom right arm hanging by side After the third collection curve there is a record of the movement of raising the hand above the head and then returning it to the side Two further collection curves follow

further increase with resting is clear and the sigmoid nature of the inflow curves is also evident

Fig 6 shows the effect of raising the arm from a hanging position at the side above the head and then returning it to the side There is no residual effect on venous distensibility which must therefore be rapidly adjustable The measured flow is greatly reduced but eventually is restored

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DISCUSSION

Burton I would like to ask Dr Whitney about the interpretation of the measurements of the girth of the arm after occlusion first with the arm level then elevated He seemed to use the same venous pressure for occlusion I should think that for comparison you would have to subtract the hydrostatic factor because after all the pressures in the vein are lower when you have the arm up therefore to compare the volume changes after collection one would surely have to lower the occlusion pressure by the hydrostatic factor

Whitney That may be so The only thing is of course that in general one really cannot measure how the hydrostatic pressure changes in different parts I thought it would be safer to keep to a uniform collection pressure and see what I got I would not like to start the business of subtracting the suitable hydrostatic pressure because it is different at all levels of the limb One might work it out but I do not think it would be very easy to do so But would any such correction really affect the general nature of the result obtained—namely that the distensibility of the venous reservoir is increased when the arm is raised from an initially lowered position?

Burton If you use 40 mm occlusion pressure let s say when the arm is level you will have a certain amount of collection before the blood slips past as fast as it is coming in and the volume will be constant Now if you use that same 40 mm. when the arm is up it would be equivalent to putting 50 mm on the arm which was level With the hydrostatic factor all the pressures are lower To get a comparable collection when the limb is down you have to use a higher venous occlusion

Whitney What do you mean by a comparable collection? We are not studying flows at all now are we because flows are not really changed by the process? We are referring to the type of curve

Burton As far as the vein goes you have to use a higher pressure to produce the same effect on that vein when it is down

Whitney I am perfectly prepared to admit that in fact that is what I was trying to prove But the point is does that record show or does it not show that when the arm is in a horizontal position the vein is in a more distensible condition? That is all I wanted to know I did not even want to know what the order of the difference was I still think I am afraid that it is in a more distensible condition when it is in the horizontal position than it is when it is lowered As was indicated in the records the act of raising or of lowering the arm did not produce a great change in the arm volume It would seem therefore that changes in the hydrostatic pressure of the blood in the veins do not result in corresponding passive changes in the volume capacity of the veins A further point is that the level of the upper arm where the occlusive pressure was applied was not greatly changed with respect to the heart when the forearm was lowered The venous hydrostatic pressure at the position of collection was not therefore seriously altered

GREENFIELD I think one of the main headaches of plethysmographers is that blood likes to collect anywhere between the cuffs other than inside the plethysmograph and it first collects in tissue outside the plethysmograph if you have an appreciable amount outside you can very easily get curves with upward concavity I think these are frequently seen *although they are not the sort of curves that people like to mention* It seems to me that one of the drawbacks of the apparatus you have described is that there is a great deal of tissue outside your measuring device and very little inside The other thing is that I think the absence of any artifact is very sinister rather than a cause for satisfaction

WHITNEY Dealing with those points in order first of all the concave curve is only obtained under certain conditions It is not obtained for example when the hand is left in circuit It is not always obtained when you put the wrist occlusion on it depends on the conditions I think *I only obtain a concave curve when the putting on of the arterial cuff* causes a drop in the venous pressure in the forearm I have a certain amount of quite convincing evidence for that The next point was that the blood does not like collecting under the gauges Well remember that these gauges are put on at a very low tension nothing like the diaphragms on plethysmographs *I am not implying that the forearm* always swells the same amount in each part (in fact I know it does *not) but the evidence that the gauge is measuring the swelling of the* forearm as a whole under natural conditions comes from two sources first of all the triple measurements to which I referred and secondly because if I put these gauges on inside an ordinary plethysmograph it is quite obvious that the arm is not swelling in the natural way at all *I am sorry I have not the evidence here but it will be presented in a* paper that is coming out

The third point was that you did not like there not being an artifact Well why should there be an artifact?

GREENFIELD Because I think that when you inflate the collecting cuff if you are taking a fair sample of everything that is happening in between the cuffs you are bound to get some displacement

WHITNEY But do you accept that *I am getting a fair record of what* is going on in the arm from the evidence of three gauges?

GREENFIELD I feel it cannot be a fair record of all the swelling in the arm between the two cuffs

WHITNEY But I can put those two cuffs in many different places with the gauge in the middle and still get no artifact In other words I have to put the cuff right up until I can see that the putting on of the cuff actually bends the skin before *I get the artifact After all what* do you suppose the artifact is but a certain amount of pressing of tissues *and blood through the veins into the plethysmograph momentarily?* Is its absence any more sinister than that?

GREENFIELD I think the absence is sinister because it is the evidence that you are only sampling part of the arm. I think the instrument is a very valuable one and extends the range of observations possible by plethysmography *I wish only to clarify its limitations*

WHITNEY I am not saying that you can always measure the volume

changes of a whole limb by a single gauge I think it can be done effectively with the forearm because I have tried the effect of setting the gauges up and down the arm I do not see the necessity in the case of the gauge method in fact it is undesirable to have the occlusion cuff pushed up into the gauge All that I want to know is how the arm swells when the venous return is blocked

Another thing which I did not have time to say anything about is the way I deduce the hand flow I first of all take the two records with the hand left in circuit i e with no wrist occlusion on and then I apply a wrist occlusion and take some more records The slopes of course usually go down Now one can use the difference between those two flows in conjunction with the volume of the hand and the forearm to deduce what the flow was through the hand and through the forearm separately on the assumption that the hand during occlusion swells exactly the same amount as the forearm. You may or may not think that is true but whichever assumption you make (and you can either assume that the hand does not swell at all as compared with the forearm or the forearm and hand swell the same amount) the difference between those two results is not as much as one might think The justification to my mind is in the evidence—you obtain hand blood flows which are very similar to those which have been obtained by the plethysmograph The advantage of this method is that the hand is not interfered with during venous collection by enclosure in an artificial environment

DORNHORST I wonder if Dr Whitney is happy that in his studies of effects of posture the skin is not moving in relation to the underlying muscle After all your gauge is attached to the skin and not muscle

WHITNEY I cannot always be sure about that of course What I feel with the records that I showed you is that the order of results is not being affected by that factor I would not say that that factor does not come in but I do not think the essential qualitative nature of the results is affected by the slipping of the skin over the muscles Of course the slipping will not be much—the gauge is very light The records which I showed you of lifting the arm and going back indicate that everything goes back in place again afterwards The sensitivity of that record is quite extreme the width of the line is equivalent to about 0.5 per cent change in volume

SHEPHERD I notice that you get a good correlation between the blood flow through the forearm as measured at various local temperatures with the gauge and with the plethysmograph Have you compared the values obtained by these two techniques following exercise of the forearm muscles or during reactive hyperæmia?

WHITNEY I have not used a plethysmograph immediately following exercise With the gauge I usually get a record about a quarter of a minute after the cessation of ordinary exercise like stepping but I do not think it is really necessary to compare the two techniques under those conditions The point is that if one is comparing the two techniques at all one is comparing them as alternative means of making physical measurements If one is doing the comparison for that purpose one is justified in choosing conditions which are suitable to both

I have put the gauge on one and the plethysmograph on the other arm but then of course one never knows if the flow in the two arms is the same even though simultaneous flows are taken I have put the gauges on inside the plethysmograph that definitely will not do because the presence of the plethysmograph certainly deforms the swelling of the arm I thought the safest thing to do was the one that I indicated in the Table i e that I would use the gauge under standard conditions which have been employed with the ordinary plethysmograph and get a statistical result and then see if the order of the measured blood flow is the same in the two cases I think you have seen that although different subjects were used in the two cases and although the two investigations were carried out by different workers (by Professor Barcroft and Dr Edholm on the one hand and by myself on the other) there was remarkable agreement in the results

DAWES I would like to ask a question concerning the whole venous occlusion technique whether plethysmograph or bracelet method Has it ever been checked in an animal with direct measurements of blood flow for example through the main arterial supply to a limb? It is very desirable that if this experiment has not been done that it should be done After all you are applying a pressure of 50 mm Hg over quite a wide area of limb and I would expect that it would upset the circulation quite considerably

WHITNEY There is a point against that argument of course You can use a variety of pressures and obtain the same blood flows With the gauge I can get the same blood flows whether I use 10 mm or 50 mm I do not know whether it is adequate evidence against the the argument that venous occlusion would affect the size of the venous reservoir

DAWES I am not asking this critically I just think it is one of the obvious simple experiments which ought to be done and I am wondering if anyone has ever done it because it goes to the whole root of this business

WHITNEY It is obvious but I do not think it is going to be simple

BARCROFT Brodie and Russell who started venous occlusion plethysmography did some experiments on the accuracy of the method They measured the renal blood flow by venous occlusion plethysmography and also directly by collection after venous outflow There was no difference between the results of the two methods

DAWES Yes but that was a special instance because only the venous outflow was measured and only the vein was occluded You are not only occluding the vein but also the lymphatic drainage and arterial supply or part of it The method should be checked if this has not been done already

BURTON May I stand up for pure logic against Dr Dawes? It seems to me that one should trust logic If at the point of the initial slope of change of volume there is no outflow—then I think it is logical that the rate of increase of volume at that point must be equal to the rate of inflow

As to your other point as to whether the cuff is altering arterial pressure we have the excellent evidence that all of us have verified

that blowing up the cuff within a certain range of different pressures gives the same results for the initial slope

There is another question in your mind I think Is there a serious reactive error? Can that initial slope be affected by something that was a reaction of the tissues of the organism to the blowing up of the cuff ? This is a matter which has often been discussed and it has been thought that it could not be a serious error Dr Gaskell now has some evidence that when the veins are full initially it definitely can be serious but I think that I would still like to rely on the logic that if there is not any outflow at the instant you blow that cuff up then the rate of increase of volume must be equal to the rate of arterial inflow with the reservation that this arterial inflow might be disturbed by a reflex

DAWES I follow your logic and I agree with it but nevertheless I think that the experiment should be done It is a small gap in the evidence which should be filled

EDHOLM Dr Dawes is one of the few people here who works on animals and I think that clearly *he* is the right person to do the experiment I hope that we shall soon hear the answer

KERSLAKE Would you be willing to apply the answer to the human after you've done it on the cat?

DAWES That is a fair comment yet I think that if this venous occlusion method can be applied successfully to animals it might give us some extremely useful results It has not been applied hitherto I suppose because people have always used anæsthetized animals

There is another point I have been worried about and that is the flow through the bone Is there very much flow through the bone and has anyone measured it?

EDHOLM A technique for measuring bone blood flow was described some years ago (Edholm Howarth and McMichael *Clin Sci* 1945) Although the method is not very precise the figures obtained are probably of the right order and are approximately 1 ml /100 ml bone/minute at a temperature of 36 C The bone flow is very considerably increased in certain diseases such as osteitis deformans and may be raised in some cases of anæmia The normal subject has a small blood flow through bone which only occupies about 10 per cent of the forearm so if the total flow is 3 0 ml /100 ml forearm/minute only 0 1 ml will be through bone

THE TRANSPARENT CHAMBER TECHNIQUE FOR OBSERVATION OF THE PERIPHERAL CIRCULATION, AS STUDIED IN MICE

GLENN H ALGIRE

MICROSCOPIC studies of the peripheral circulation in mammals usually are limited to acute short term experiments under anæsthesia as in the cheek pouch of hamsters or in the ears or mesentery of rats and mice The transparent chamber technique first introduced by Sandison (1924) and Clark (1930) some twenty five years ago made use of the rabbit ear for observations of either preformed or newly formed vessels in unanæsthetized animals over periods of months or years We have modified these procedures for use in various problems of cancer research in which mice have been the experimental animal (Algire 1943 Algire and Legallais 1949)

A transparent chamber may be introduced into a skin fold of a mouse as shown in Fig 1 The operative part is carried out under nembutal anæsthesia requiring less than one hour Observations may be made under the microscope immediately thereafter as indicated in Fig 2 and daily for the duration of the preparation This procedure permits observation for periods of from 30 to 60 days of the tissues and the blood supply of a layer of skin 0 5 mm thick by 14 mm diameter Within this tissue one finds the peripheral nerves and a thin layer of striated muscle close to the cover slip with the dermis and epidermis in the adjacent layers

Several choices are presented for studies of either transplanted tissue or of the peripheral circulation as shown in Figs 3 6 The preformed tissue type with dermis and a thin layer of striated muscle is approximately 500 micra in thickness In the central table design a thin layer of striated

FIG 1 Mou e ith transp rent chamber in dorsal sk n fold

FIG - Mou e ithin holder in position o microscop t e

FIG 3 Tissue within transparent chamber showing blood vessels lymphatics and early vascularization of sarcoma tissue (arrows) (five days after implantation) × 20

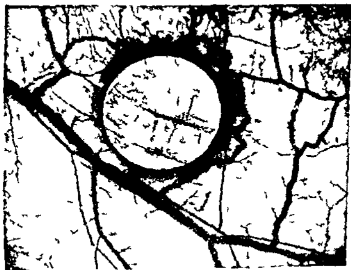


FIG 4 Surface view showing tissue within round table type

FIG 7 Cross striation in regenerated muscle within round table type chamber × approx [illegible]



FIG 8 Platelets in circulating blood as seen in profile and as flat plates Enlargement from 16 mm movie film original

muscle 50 to 75 micra thick may be observed at high magnification with resolution of fine structural details Alternatively a space of from 25 to 50 micra is provided into which new capillaries and cells may migrate or striated muscle may regenerate (Fig 7) or circulating platelets may be seen (Fig 8)

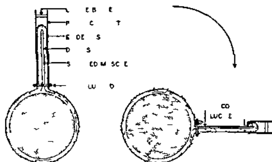


FIG 5 Relationship of transparent chamber to skin fold

TANTALUM STUD
STRIATED MUSCLE
COVER SLIP
LUCITE RING
DERMIS
EPIDERMIS
TRANSMITTED LIGHT
A

TANTALUM STUD
SPACER
GLASS DISK
COVER SLIP
LUCITE RING
DERMIS
STRIATED MUSCLE
EPIDERMIS
LUCITE RING
NUT
TRANSMITTED LIGHT
B

FIG 6 Cross section of (A) preformed and (B) round table type transparent chambers

Green (1948) and others have correctly observed that increased significance can be attached to conclusions drawn from microscopic observations of blood vessels when such studies are combined with simultaneous determination of other circulatory phenomena. In this account of our work, therefore, I shall place greatest emphasis on methods by means of which we have tried to move in this direction.

Our initial excursions into problems of the peripheral circulation centred around an interest in the mechanism of action of certain chemical agents which, upon subcutaneous or intraperitoneal injection, had been noted by various workers to produce hæmorrhage and necrosis in transplanted tumours. It became increasingly apparent to us that some of these agents damage tumours not through a specific effect on the cancer cells, but indirectly as a result of their hypotensive effects on the host.

Intraperitoneal injection of a bacterial polysaccharide preparation from *Serratia marcescens* into a mouse carrying a transplanted sarcoma within the transparent chamber results in decreased blood flow in capillaries of both the tumour and the surrounding striated muscle (Algire, Legallais and Park, 1947).

These circulatory changes were observed within two hours after injection, and were followed at the end of four hours or more by hæmorrhage within the tumour and one day later by necrosis of the central area of the tumour.

A method of random sampling devised by Chalkley (1943) of the National Cancer Institute enabled us to express these events in a relatively quantitative way. In this method the object field as viewed through the microscope is presented at random to a pattern of points in the ocular diaphragm. Each intercept of point and vessel is counted as a "hit". Random presentation of field to pointers for 100 times provides a statistically valid sample for estimation of the percentage of vascular tissue.

Further analysis of these reactions became possible after devising methods for indirect measurement of blood pressure

(Algire 1949) This procedure in principle is identical to that used by Roy and Brown (1880) Using this method it was found that maintenance of capillary blood flow was dependent upon blood pressure The theoretical basis for the dependence of capillary circulation on blood pressure has been reviewed by Burton and Yamada (1951) and its impli

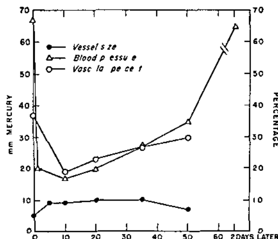


FIG 9 Graph showing effect of histamine on blood pressure vascular percentage and vessel size (15 mg intraperitoneal injection)

cations for tumour circulation discussed by Algire and Legallais (1951)

The effects of intraperitoneally administered histamine on capillary blood flow in both striated muscle and transplanted sarcoma were the same as related above (Algire and Legallais 1951) (Fig 9)

It is noteworthy that capillaries in striated muscle and in subcutaneous connective tissue showed greater resistance to irreversible damage from the effects of prolonged hypotension than did those in sarcomas or in granulation tissue The cessation of muscle contraction during periods of hypotension

however, indicated a response to the altered tissue metabolism This is further borne out by observations of vasomotor activity of arterioles in striated muscle The frequency and duration of each phase of vasomotion may be quantitatively recorded using an intervalometer These determinations may be correlated with changes in blood pressure as measured at the same local site and with changes in blood flow and heart rate Under conditions of normal blood pressure the arterioles in striated muscle may be constricted *i e* completely closed for periods of from 17 to 70 per cent of the time (Algire unpublished experiments)

Vasomotor activity ceased when blood pressure increased or decreased Spontaneous vasomotor activity is thus quite responsive to blood pressure changes In studies of the effects of intravenously injected substances on vasomotion, changes in blood pressure at the site of observation should be taken into account before inferring direct influence on the reactivity of the terminal arterioles

Highly diffusible dyes such as fluorescein quickly become evenly distributed throughout well vascularized tissues but pass slowly into non vascularized or necrotic tissue With the passage of time the dye gradually spreads into the poorly vascularized areas so that these also eventually become fluorescent (Algire unpublished experiments) On the other hand removal of the dye through the blood stream and lymphatic drainage is more rapid from well vascularized than from necrotic or avascular areas Consequently one will find a time after injection when dye is present in higher concentration in the avascular areas than elsewhere In this differential rate of uptake and release of the dye one finds I believe an explanation for the observation of Moore (1947) that fluorescein localizes in certain tumours about three hours after injection

In conclusion the plea of Krogh (1929) for the study of quantitative anatomy as a basis for quantitative physiological studies is no less valid now than twenty five years ago Large gaps exist in our knowledge of the functional length of

capillaries in various tissues maximum diffusion distances rates of flow and permeability Recent technical advances by many workers make these problems accessible to quantitative investigation at the microscopical level

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DISCUSSION

WEDDELL Do you find it easy to recognize arterio venous anastomoses?

ALGIRE These have been observed in the peripheral nerve trunks where they are spaced at intervals of approximately one millimetre I have been interested in that because the nerve trunk except for the main artery and vein carries very little capillary blood and it seems that a great deal of its nutrition must come by diffusion from the adjacent richly vascularized striated muscle

WEDDELL Did you see any in the muscles or other tissues which you examined?

ALGIRE No I have not seen any except in the nerve trunks *

WEDDELL You did say that you could see capillaries growing without necessarily having any pressure behind them?

ALGIRE Yes that may occur and as Dr Burton mentioned in his review it has been seen in tissue culture preparations also

WEDDELL This would seem to dispose of the idea that capillaries only grow because the internal hæmostatic pressure exceeds that in the

Addendum Since returning from the conference A–V anastomoses have been found in striated muscl (panniculus carnosus) Their frequency and d stribution is not y t cl a

tissues in which they lie You mentioned that you could recognize nerve trunks and also smaller nerve fibres but you said these were difficult to see How fine a nerve fibre could you see?

ALGIRE I think one would have to use vital dyes to be sure of that

WEDDELL *In unstained preparation then is it very difficult to distinguish small nerve bundles?*

ALGIRE I think that with a special effort to concentrate on nerves one could do much on the finer nerve terminals but I have not as yet done that

BURTON Dr Algire would you consider that this method of estimating the local blood pressure as you called it is in effect measuring the pressure? Does it not depend just as much on the tone of those small vessels? I mean it is exactly the method by which we think we can measure the critical closing pressure which is a measure of the tone of the vessels This measurement gave you a blood pressure" much less than 100 mm Hg I wonder whether the actual pressure in the large arteries of the mouse was not still up near 100 mm Do you really feel that the central blood pressure dropped to those levels or is not this method measuring just as much the tendency of those vessels to close as the pressure within them?

ALGIRE It is true that measurements of blood pressure by an indirect method of this type are influenced both by the tone of the vessel and by the hæmodynamic pressure However the relative values obtained by this method are supported by visual evidence of a decrease in rates of flow during hypotension as indicated by the change from laminar or stream lined flow to a granular type of flow in which the cellular elements become visible Therefore I do not think that alterations in vasomotor tone alone could account for the pressure required for occlusion of the vessel by this indirect method It would be useful to have measurements of the central blood pressure as well but we have not yet done this

HERTZMAN *I should like to ask about a possible criterion of injury to the vessels in connection with making preparations like this* Years ago with a very limited type of technique I had occasion to put windows in the skull which remained for ten weeks Particularly in the rabbit we saw vessels balloon out apparently for no reason and then that ballooned portion would constrict back again It would remain ballooned for hours The dog never showed that type of vascular response *We supposed at the time that there were differences in the* susceptibility of the vessels to injury Have you seen anything like that?

ALGIRE There are various reactions to injury that one sees There may be constriction of the artery or local constriction with dilatation nearby as shown in Dr Burton s slides this morning One also sees in injury to the blood vessels that on of the earliest indications of an inflammatory reaction is the attachment of leucocytes to the vessel wall with more severe injury *the large white emboli of leucocytes and* (or) platelets develop and are swept away into the circulation

DIBLE You said that the new capillaries developed in the implant I have seen the same sort of thing developing in what is apparently an

inert blood clot—in thrombi—and it seems that these capillaries develop from histiocytes as you say they do not originate by the process of budding from pre existing capillaries The ones you see do you think they develop from pre existing capillaries in the implant or do you think they develop from undifferentiated histiocytes?

ALGIRE They develop from the pre-existing endothelial cells within the implant We can see blood cells trapped in vessels within the implant and we can watch the outgrowth from some of those areas We have done experiments with embryonic thyroid tissue in which blood vessels have been seen to grow out from one to the other neither of them having connection to the host but nourished simply by diffusion

DIBLE But I suppose they ultimately develop a connection with the host?

ALGIRE They usually do However Dr Ruth Mervin in our laboratory has devised a technique to maintain a small implant surviving by diffusion without any blood supply at all so that a small implant of thyroid or other tissue may be placed within the chamber separated by a connective tissue barrier from the underlying blood vessels Under those conditions even homografts will survive indefinitely

DIBLE When they ultimately develop connections with the host what is the process by which they link up with the host s vessels? Also what determines how they evolve subsequently that is whether they develop into arterioles or venules?

ALGIRE The intimate details of the connection in the host we do not know yet but I think Clark s studies on rabbit ear chambers are most detailed in that respect The factors determining the differentiation into arterioles and venules are probably largely based on pressure differences some capillaries disappear and others develop vasomotor activity indicating that they are no longer true capillaries but have become arterioles with smooth muscle

GRANT You mentioned that you see arterio-venous anastomoses there Have they a specialized structure e g like that of the anastomoses of the human finger?

ALGIRE There is nothing that we can see except that the connections are quite large and much larger than the true capillaries which are about six microns in diameter These are of the order of 30 to 40 microns or larger

VON EULER Was it possible to show any specific pharmacological action of adrenaline on these arterio venous anastomoses? I mean did they react in any way differently from the other arterioles?

ALGIRE I have seen no indication that they react differently They *seem to respond to adrenaline* as others do but I *have not made* any extensive study of that

GASKELL. Can Dr Algire give us any idea of the pressure at which capillaries arteries and veins close? If I remember correctly Roy and Brown found that the capillaries closed first Do you agree with that?

ALGIRE This indirect method is not considered sufficiently accurate to determine other than relative values or changes in pressure within a single vessel The values obtained however are in accord with the

Table I (Algire)

DETERMINATIONS OF BLOOD PRESSURE AND VESSEL DIAMETER IN PERIPHERAL VASCULAR BEDS AS AFFECTED BY HYPOTENSIVE OR HYPERTENSIVE PROCEDURES

Exp No	Exp Procedure	Reading	Artery 1	Artery 2	Artery 3	Artery 4	Precapillary Artery	Cap	C p	Venous Capillary	Venule 1	Vein
1	Normal	B P	95	55	90	60	35	[illegible]	20			
		Diam	07	08	07	03	005	005	006			
2	Normal	B P	80	65	45	30	28	25	22	17	18	8
		Diam	06	05	05	01	005	006	006	01	02	04
3	Normal	B P	6	55	45	40	30	27		10	18	
		Diam	07	03	03	01		005		005	06	
4	Control	B P	82	60	48	33	26	15		11	18	25
		Diam	05	03	03	02				01	04	05
	After accidental dehydration and starvation	B P	75	27	25	20	12			4	4	
		Diam	07	04	04	01	005				03	
5	Control	B P	60	50	35	30	30					
		Diam	07	04	03	03	005					
	Adrenaline subcut 0 1 mg	B P	90	70	45	35						
		Diam	07	0	04	03						
6	Control	B P	9	90	90	45	2					
		Diam	08	00	06	01	005					
	10 mg histamine (i p)	B P	40	3	2	20	15					
		Diam	06									
	Recovery (next day)	B P	90	85	80	42	25					
		Diam	05		04		00					

Blood pressure is expressed in millimetres of mercury and vessel diameter in millimetres

direction of blood flow as one scans successive branches of an artery arterioles capillaries and venous capillaries Discrepancies between observed measurements and the direction of flow appear however when one passes to the venules and veins where the increased vessel diameter low pressures result in obvious artifact

Table I gives an indication of the range of values obtained in following blood pressure levels through an artery and its branches to the venous side of the vascular bed It is apparent from this table that the venous capillaries close at lower pressures than the true capillaries but that artifacts appear as one passes the venules and veins With reference to the paper of Roy and Brown these authors did not measure capillary pressure as indicated in the following excerpt from their articles We have in fact no means of learning with certainty the blood pressure in a given point of a given capillary We can readily find the pressure in the terminal arterioles and approximately the pressure in the venous rootlets but the exact distribution of the pressure in the intervening capillaries can only be roughly judged by noting the order in which these collapse on raising the extravascular pressure When therefore the intracapillary pressure is spoken of in the pages of this communication it must be understood that we are not referring to any given value which it is possible to measure

The capillaries close first In fact the chief thing one notices is the collapse of the capillary blood supply As the pressure drops the capillary blood flow becomes slower and finally one reaches a point where there is complete stoppage and in many cases complete disappearance of the capillaries as their wall come together

Gaskell Does that occur when it is obvious that the veins and the arteries in the area are still open?

Alcire Yes

Burton That proves surely that you cannot just be measuring the pressure within them by noting the pressure at which they collapse it depends on the tone of the vessels also The veins must be at a lower pressure than the capillaries yet the capillaries close first

DIFFERENTIAL SECRETION OF ADRENALINE AND NORADRENALINE FROM THE SUPRARENAL GLAND

U S von EULER

It is well known by now that adrenaline and noradrenaline differ in their biological actions in several fundamental respects This is true not only for the effects on the circulatory system but also for the metabolic actions Considerable evidence has indicated that noradrenaline is the chief ergone for maintaining blood pressure homeostasis while adrenaline is far more active in stimulating a variety of metabolic functions related to the defence mechanisms in conditions of stress

This functional differentiation raises the problem as to the underlying mechanisms for the release from the suprarenal gland of one or the other of the hormones Numerous studies of the catechol amine content of the suprarenal medulla have demonstrated that in the same species the relative amounts of adrenaline and noradrenaline normally are remarkably constant and quite characteristic for that species Such a fact indicates that there must be an extremely delicate mechanism for maintaining the balance in the production of the two substances if they are manufactured in the same cell or else they must be produced separately *i e in different* kinds of cells

One approach to this problem would obviously be to determine whether various kinds of stimulation released one or the other of the two catechols separately or as a mixture more or less proportional in amount to the content of the two amines in the suprarenal gland Another way would be to establish the presence of two kinds of cells in the gland and prove that they are selectively engaged in the production of either one or the other hormone

The possibilities of studying a differentiated secretion of adrenaline and noradrenaline by determining their content in the urine are not favourable since it is difficult to be certain how much noradrenaline is derived from the adrenergic nerves and what quantity comes from the adrenal medulla. The only way to obtain conclusive data on this point would be by the direct estimation of the catechol amine content of suprarenal venous blood.

Using a two test biological method Brucke, Kaindl and Mayer (1952) were the first to show that the catechol amine composition of the resting secretion in the cat differed widely from that obtained during hypothalamic stimulation. They found a relative adrenaline content of about 11 per cent in the resting secretion as compared with about 50 per cent adrenaline during hypothalamic stimulation. It might be argued that since the resting secretion was quantitatively less than the secretion during stimulation this might have influenced the composition. Kaindl and Euler (1951) have shown, however, that although carotid occlusion increased the total catechol secretion about four times there was no accompanying shift in the percentage of noradrenaline or adrenaline released.

Moreover, Holtz *et al.* (1952) found that splanchnic stimulation released what appeared to be almost pure adrenaline in the cat. Outschoorn (1952) and Vogt (1952) stated that various kinds of stimulation of the gland did not cause appreciable alteration in the relative amounts of the catechols in the secretion. However, the types of stimulation used in their experiments were not particularly suited to reveal a possible selective secretion.

Assuming that a selective secretion of the two catechol amines in the suprarenal medulla would be likely, Euler and Folkow (1953a) studied the output during various conditions in the cat. Adrenaline and noradrenaline were estimated by direct testing of the heparinized suprarenal venous plasma on the cat's blood pressure and the rectal cæcum of the hen as customary in our laboratory.

Blood samples were collected during carotid occlusion and during stimulation of the central end of the cut sciatic or brachial plexus Both types of stimulation were chosen since carotid occlusion was known to stimulate the noradrenaline secretion while afferent stimulation of the other nerves might be expected to stimulate adrenaline secretion In 11 experiments, the adrenaline percentage was invariably higher in the latter type of stimulation The absolute figures of catechol secretion expressed in μg /kg /minute (from one suprarenal) showed large variations in both types of stimulation as did the relative adrenaline content However the difference in adrenaline percentage between the two types of adrenal medullary stimulation was significant If the relationship between the adrenaline percentages for the two kinds of stimulation was determined in the same animal the difference was very clear as seen in Fig 1 (Euler and Folkow 1953a)

These observations indicate a difference in the composition of the catechol amines coming from the suprarenal medulla depending on the type of reflex stimulation In a few experiments the spontaneous secretion and the effect of asphyxia or splanchnic stimulation was also studied No statistically significant difference was found between the adrenaline percentage in these cases and during carotid occlusion The results seem to warrant the conclusion that sciatic or analogous stimulation leads to a reflex release of adrenaline perhaps through nociceptive fibres

Duner (1953a) in our laboratory has recently studied the influence of the blood glucose level on the release of catechol amines from the suprarenal There is ample evidence obtained by various methods that hypoglycæmia evokes an increased adrenaline secretion (Cannon McIver and Bliss 1924 Houssay Molinelli and Lewis 1924 Hokfelt 1951 Outschoorn 1952 Euler and Luft 1952) In his experiments Dunér produced a hyperglycæmia by injecting glucose in the cat and found a considerable reduction in the adrenaline secretion but only a small decrease in the noradrenaline secretion He also found that this selective effect could be

obtained by a local hyperglycæmia in the head while hyperglycæmia in the rest of the body was without effect on the catechol secretion Hypoglycæmia on the other hand caused a selective increase in the adrenaline secretion (Duner 1953b)

With this background it seemed of interest to repeat the results of *Brucke and co workers In a series of experiments*

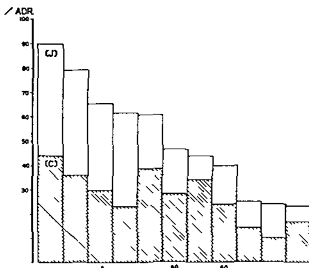


FIG 1 Percentage adrenaline in suprarenal venous blood in the cat during carotid occlusion (striped part of column C) and during sciatic or brachial plexus stimulation (whole column J) in each of 11 animals Relation in per cent below each column (Mean 5 4 per cent ± 4 1) (From U S Von Euler and B Folkow Arch exp Path Pharmak 19 3 in the press)

(Euler and Folkow 1953b) it was found that hypothalamic stimulation in the cat caused a higher adrenaline percentage in the suprarenal catechol secretion than during spontaneous secretion or carotid occlusion this confirming Brucke Kaindl and Mayer (1952) However in one experiment the reverse was true hypothalamic stimulation yielding almost pure noradrenaline In this experiment the stimulatory

electrode had unintentionally been inserted at a different place in the hypothalamus

In continued experiments it became clear that stimulation of some parts of the hypothalamus regularly produced almost exclusively noradrenaline while other points on stimulation released large amounts of adrenaline

Thus it seems clearly demonstrated that noradrenaline and adrenaline can be selectively released at least to a certain extent depending on the site of hypothalamic stimulation One is then led to postulate the presence of areas in the hypothalamus from which specific secretory fibres reach the suprarenal medulla

Several mechanisms by which certain nerve fibres activate either noradrenaline or adrenaline secretion are possible If the medullary cells are all of the same kind one would have to assume that the degree of methylation is controlled by *nervous impulses alone It is difficult to see how nerve acti*vation of a cell at least if it is obeying the all or none principle could be capable of producing such a balanced and delicate control on the enzymatic activity of the cell Obviously stimulation by nerve impulses on two types of cells would explain more readily such a differentiated secretion The independent release of one or the other hormone by reflex or direct stimulation would then mean that each specific cell has its specific innervation and that one should expect to find two kinds of secretory fibres in the splanchnic One of the arguments in favour of an undiscriminating action of nervous stimuli on the medullary cells has been the lack of morphological or chemical evidence for different kinds of cells in the adrenal medulla Recently however Hillarp and Hokfelt (1953) have demonstrated two kinds of cells in the mammalian adrenal medulla one of them forming pigment from noradrenaline It thus appears that the physiological evidence for a selective activation of noradrenaline or adrenaline producing cells has obtained a histochemical basis

The importance of the demonstration of a differentiated adrenal medullary secretion of adrenaline or noradrenaline to

the peripheral circulation in man is that the release of either catechol can be adjusted to meet the homeostatic requirements Although a direct demonstration of an independent secretion of one or the other hormone from the adrenal medulla may be difficult to achieve in man the regulation of blood pressure may well necessitate a release of noradrenaline under certain conditions while situations of stress are likely to bring about an increased production of adrenaline

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DISCUSSION

HERTZMAN Dr Cox and Dr Cooper have obtained some data in my laboratory on the action of adrenaline and noradrenaline on the toe pad vessels of the dog Your data indicates that noradrenaline would be the substance which ought to be released in the service of vasomotor activity In the case of toe pad vessels the threshold dose for adrenaline is lower than that for noradrenaline at any equal concentration injected into the blood stream the action of adrenaline is stronger I think that is an interesting observation because these vessels are very peculiar in many respects in their behaviour but it is just the reverse of what seems to be the common impression in respect to their actions

VON EULER I think this is in keeping with the results of Dr Whelan the sensitivity of the vessels in the skin is higher for adrenaline than it is for noradrenaline quite independently of the fact that noradrenaline

is the mediator of the vasomotor nerves The skin of the hands the face and the feet are rather specific vascular areas and there may be others more sensitive to adrenaline than to noradrenaline

BURTON Would you care to speculate about the possible role of the adrenal cortex in the methylation? I have heard it put forward that the degree of methylation might be determined by the hormones of the adrenal cortex *Is there any evidence for this?*

VON EULER I think the idea was first expressed by West but as far as I know it has been withdrawn There is not sufficient evidence to substantiate it The only thing I can say is that slices which are very carefully cut out of the cortex where there is no branching out of the medulla contain small amounts of catechol amines in somewhat varying proportions as shown by Batty and Hokfelt in our laboratory

BURTON I think I have heard you mention something about cortisone reversing the proportions of adrenaline to noradrenaline?

VON EULER Yes there seems to be a certain shift in the proportions of catechol amines in some organs

DALE Is there any evidence of a possible differential sensitiveness in the two different kinds of medullary cells to any preganglionic trans mitter? When you give a shot of intra arterial acetylcholine does the proportion between adrenaline and noradrenaline coming out of the gland shift from the resting value?

VON EULER We do not know that is a very interesting question indeed It may be that adrenaline produces some transmission block if introduced in sufficient quantities

EDHOLM Is there any evidence of species differences in response to adrenaline or noradrenaline corresponding to the very varied propor tions of the two in the suprarenal gland?

VON EULER I think one can say that the rabbit is relatively speaking not very sensitive to noradrenaline and has usually none in its supra renal medulla On the other hand the vasomotor nerves even of the rabbit seem to produce noradrenaline

THE EFFECT OF ADRENALINE AND NORADRENALINE ON THE BLOOD FLOW THROUGH HUMAN SKELETAL MUSCLE*

R F WHELAN

Adrenaline

Adrenaline affects the blood flow through human skeletal muscle in two ways—direct and indirect The direct action of the drug causes a transient vasodilatation while the indirect action produces a sustained increase in flow These effects have been established by intravascular infusions of adrenaline with measurements of the blood flow through the forearm and calf by venous occlusion plethysmography Since the action of adrenaline on skin vessels is to cause a constriction any dilator response must be in the underlying muscle Fig 1A shows the effect on the blood flow through the forearm of an infusion of 1/20 μg of adrenaline per min into the brachial artery There is an initial transient dilatation in the first two minutes but the flow throughout the remainder of the infusion is little different from the resting level The indirect effect is seen in addition when the adrenaline is administered by the intravenous route in comparable doses (10 20 μg/min) (Fig 1B) Following the initial transient vasodilatation the flow settles to about double the resting value and is maintained at this level throughout the remainder of the infusion even when this is prolonged for an hour or more These patterns of response of the muscle blood flow to adrenaline have been described by various authors including Allen Barcroft and Edholm (1946) and Duff and Swan (1951)

* The work to be described on adrenaline was carried out at the Sherrington School of Physiology St Thomas s Hospital London That on noradrenaline was done in collaboration with Professor H Barcroft and Dr P Gaskell at St Thomas s and Dr J T Shepherd at the Queen s University of Belfast

As yet we do not know by what mechanism the sustained increase in forearm flow seen during intravenous adrenaline is brought about It is not mediated by the sympathetic nervous system If the deep nerves to one forearm are blocked with local anæsthetic the flow in that forearm is about double that of the control side due to the release of sympathetic tone but the pattern of response is not otherwise altered (Fig 1c) Similarly when adrenaline is given intravenously to a patient within the first few weeks after cervical sympathectomy the typical dilator response is still obtained (Fig 1D) The dilator effect in these cases becomes diminished and may disappear with the development of the chronic state (Duff and Swan 1951 Whelan 1952) This latter phenomenon may be related in some way to the gradual return of tone in the vessels of the upper limb demonstrated by Barcroft and Walker (1949)

The sustained dilatation is not a consequence of the hyperventilation produced by the adrenaline infusion because it does not occur during a comparable degree of hyperventilation alone (Dornhorst and Whelan 1952 Whelan and Young 1953)

The increase in flow is not due to a rise in the perfusion pressure in the limb because the increase in mean pressure produced by 10 20 μg/min of adrenaline is slight the systolic pressure being raised while the diastolic pressure falls (Barnett Blacket Depoorter Sanderson and Wilson 1950 Duff and Swan 1951) and would be insufficient to account for the 100 per cent increase in flow

Since the sustained dilator effect of adrenaline on the forearm is not a direct effect of the drug on the muscle vessels is not mediated by the sympathetic or somatic nerves and is not a result of the accompanying hyperventilation nor the changes in blood pressure other possibilities must be considered When adrenaline is administered intravenously it may become modified in some way during its circulation through the body or it may release some other vasodilator substance from an internal organ or endocrine gland which

on reaching the forearm produces the increase in flow. Such a change or release would not occur when the adrenaline is infused intra arterially and could account for the difference

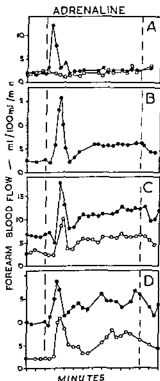


Fig 1 Intravascular infusions of adrenaline. Forearm blood flow measured by the water filled plethysmograph at 34 C. A saline infusion was maintained throughout each experiment. Adrenaline made up to *the required concentration in saline* was infused for the periods indicated by the vertical interrupted lines.

(A) Infusion at 1/[illegible]0th μg/min into the left brachial artery at the elbow. ● *Left forearm* ○ *right forearm (control)*

(B) Intravenous infusion at 10 μg/min. Normal forearm

(C) Intravenous infusion at 10 μg/min. ● nerve blocked forearm ○ control forearm

(D) Intravenous infusion at 10 μg/min. ● sympathectomized forearm ○ same forearm prior to operation

between the effects of the two methods of infusion Staub (1946) found an increase in the level of plasma histamine during intravenous infusions of 20 μg/min of adrenaline and suggested that some of the effects of adrenaline could be produced by the circulating histamine Mongar and Whelan (1953) however have not been able to confirm the observations of Staub and could not detect any increase in the plasma histamine level with infusions of adrenaline whether intravenous or intra arterial

Long (1947) and McDermott Fry Brobeck and Long (1950) demonstrated that adrenaline stimulates the release of adrenocorticotrophic hormone and thyrotropin from the anterior pituitary gland and it is conceivable that release of thyroid hormone could be responsible for the muscle vaso dilatation though the rapidity of the response would make it appear unlikely The response to intravenous adrenaline of *the forearm flow in a thyrotoxic patient appeared to be* greater and in a myxœdematous patient to be smaller than the normal (Whelan unpublished) Much more work however, will be necessary before the role of other endocrine secretions in the response of the body to adrenaline is determined

Noradrenaline

Noradrenaline also has a dual effect on muscle vessels Fig 24 *shows the response of the forearm blood flow to an* intra arterial infusion of 1/20 μg/min of noradrenaline There is a decrease in flow to about one third of the resting level usually sustained throughout the infusion Such a fall is not accounted for by the skin constriction alone (Barcroft and Konzett 1949) and is therefore largely a direct effect of noradrenaline on the muscle vessels

When noradrenaline is infused intravenously the response in the forearm is different from the above (Barcroft Caskell Shepherd and Whelan 1953) There is often an initial transient increase in flow *and following this little change or* an increased flow of 30–50 per cent above the resting level

(Fig 2B$_1$) Sometimes there is a sustained increase in flow (Fig 2B$_2$) A fall in flow is not seen in the forearm in spite of the constriction of the skin vessels as evidenced by pallor of the face and a fall in hand blood flow (In the case of the calf a small fall in flow is sometimes seen possibly due to a predominance of the direct constrictor effect of the drug)

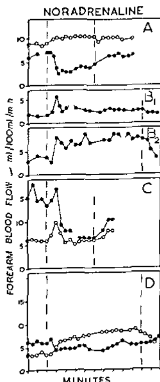


FIG 2 Intravascular infusions of nor adrenaline

(A) Infusion at 1/10th μg/min into the left brachial artery ● Left forearm ○ right forearm (control)

(B B) Intravenous infusions at 10 μg/min Normal forearms

(C) Intravenous infusion at 10 μg/min ● nerve blocked forearm ○ control forearm

(D) Intravenous infusion at 10 μg/min ● sympathectomized forearm ○ control forearm

The indirect dilator effect of intravenous noradrenaline on the forearm is abolished and a constriction occurs if the deep nerves are blocked with local anæsthetic (Fig 2c) or if the arm is sympathectomised (Fig 2D) The fact that the usual increase in flow is seen at the same time in the opposite control forearm indicates that the increase is not produced by an associated rise in the perfusion pressure in the limb as a result of the increase in mean blood pressure The dilatation is not a result of the hyperventilation associated with the noradrenaline administration because it is not seen with a controlled hyperventilation of a comparable degree

The sustained dilator response to noradrenaline is thus mediated by the sympathetic nerves The central effect producing this sympathetic dilator action might be a direct action of noradrenaline on the vasomotor centre or might be due to the rise in blood pressure acting via the carotid sinuses and vasomotor centre The resulting vasomotor action might be either release of sympathetic tone or might involve active vasodilatation (Barcroft and Edholm 1945) Which of the possible mechanisms is involved is yet to be decided

Summary of Effects of Adrenaline and Noradrenaline on the Forearm Muscle Blood Vessels

Adrenaline

(a) Direct effect—a transient vasodilatation
(b) Indirect effect—a sustained vasodilatation the mechanism of which is unknown but is not mediated by nerves

When adrenaline is given intravenously both these effects are seen

Noradrenaline

(a) Direct effect—a sustained vasoconstriction
(b) Indirect effect—a sustained vasodilatation mediated by the sympathetic nervous system

When noradrenaline is given intravenously the dilator effect usually predominates

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DISCUSSION

VON EULER Is it possible that this sustained vasodilator effect by adrenaline could have anything to do with the formation of lactic acid? Lundholm has recently claimed that adrenaline causes vaso dilatation by producing lactic acid

WHELAN I suppose that is possible but I have not made any measure ments on blood lactic acid The arterial infusions would rather be against it though unless the lactic acid is being produced in the lungs or elsewhere and then circulates If you inject adrenaline intra arterially you do not get the sustained increase so that it must be due to something which is being released somewhere else and is carried to the forearm in the arterial blood

ASMUSSEN There is a general increase in blood lactic acid when you inject adrenaline intra muscularly it appears about the same time as glucose and would account for the hyperventilation perhaps It corres ponds beautifully with von Euler s observations that adrenaline has these metabolic effects

EDHOLM What concentration of lactic acid is released with these doses? In some experiments in connection with liver blood flow an infusion of adrenaline similar to that used by Dr Whelan provided only a small change in lactic acid

ASMUSSEN As the experiments I was thinking of were made about fifteen years ago I do not remember the actual figures but I seem to remember from the curve that the level was at least double the resting level of lactic acid

EDHOLM I believe you were using rather larger doses of adrenaline

ASMUSSEN But they were given intramuscularly

BARCROFT Some time ago Dr Sherlock did some experiments on lactic acid given intra arterially The very odd fact emerged that she could not find any increase in lactic acid in the venous blood She was not able to explain this

DORNHORST In the experiments done on the hyperventilation with a dosage of about 10 to 20 gamma a minute there is an actual rise rather than a fall in the CO_2 binding power of the blood which suggests that there is not much lactic acid present

DALE Is there any direct evidence that lactic acid in the kind of concentration which is under discussion does in fact produce an increase in the blood flow?

BURTON I remember experiments in which the effect of *p*H on the perfused limb was followed and quite unexpectedly it was found that *if you go either way from the neutral point of blood the blood flow* increases It takes a very small change of the *p*H (from 7 4) on the acid or the alkaline side to get a marked increase of blood flow

DALE The *p*H—that would be an artificial perfusion scheme would it?

BURTON Yes

DAWES What happened to the blood pressures during these intravenous infusions? Vass and his colleagues showed in cats that the secondary increase in blood flow was due to the rise in blood pressure after intravenous infusion of noradrenaline

WHELAN Infusions of 10 to 20 micrograms per minute of adrenaline increase the systolic pressure by about 10 to 15 mm Hg with a fall in *diastolic The mean pressure does not alter more than perhaps mm* Such an increase in mean pressure could not account for the 100 per cent increase in forearm blood flow Professor Barcroft agrees with this

HERTZMAN It seems to me your key experiment is the one in which you got reversal of the action of noradrenaline after blocking That would eliminate lactic acid wouldn t it?

WHELAN Yes The sustained increase with the adrenaline might be due to lactic acid but this is not the case with noradrenaline With noradrenaline the dilatation is mediated via the sympathetic nerves

BURCH What has happened to the cardiac output (not necessarily from your experiments as you may not have measured it but from what we know) at that time? Secondly what is happening to other structures besides the muscle—is this phenomenon limited entirely to muscle or is it apt to occur in the arteries of other viscera?

WHELAN Professor Barcroft is in a better position to answer the first question than I am

BARCROFT The cardiac output has been estimated by Goldenberg and his colleagues by the Fick method using approximately the same adrenaline dosage Taking their results as a whole adrenaline increases cardiac output by approximately one third It also causes an overall peripheral vasodilatation Noradrenaline has the reverse effect There is a decreased cardiac output and an overall peripheral vasoconstriction Goldenberg s results accord very well with those obtained by Dr Isaac Starr and myself with the ballistocardiograph

WHELAN With regard to other organs apart from skin there is little evidence skin constriction occurs in the hand of course Dr Edholm has done some work on these lines

EDHOLM Dr Sherlock and her colleagues followed the changes in liver blood flow during the intravenous infusion of adrenaline and nor adrenaline They used the bromsulphthalein technique so hepatic blood flow could only be measured at intervals of five minutes or longer Hence it would not be possible to determine the presence or absence of an after effect as described by Dr Whelan Such determinations as were made did not indicate any significant after effect

BURCH The reason I asked the question about cardiac output is that if the cardiac output does not change when there is an increase in flow in muscles there would probably be shifting of blood from some other organs Thus if there is vasodilatation in all the organs the cardiac output would have to rise to explain the findings

WHELAN Adrenaline causes an increase in heart rate of course and noradrenaline a slowing of the heart

BURCH Could you estimate what might be happening to the cardiac output?

WHELAN I do not think so The increase in cardiac output with adrenaline is partly due to an increased stroke volume and partly to the increase in rate

DORNHORST The rate is about 100

WHELAN It starts at about 100 and then it tends to come down a little and settles to a steady rate of about 80

EDHOLM The cardiac output as Professor Barcroft said would be raised about 30 per cent or 40 per cent which could more than account for this increase in fact it leaves a good deal over for other organs

DAWES I should like to raise two other points They concern the change in pulse pressure which I understand does occur It is so ea y to say that since the mean pressure does not vary the fact that the pulse pressure has changed means that no significant change has taken place in the body as a whole I would like to ask Professor Burton first of all if you were to get a large increase in systolic and a corresponding decrease in diastolic blood pressure so that your mean pressure was the same will flow take place through a peripheral system whose peripheral vascular resistance has not been altered? The second point is what effect has this change in pulse pressure on the carotid sinus and aortic stretch receptors? Would it make them fire off more frequently during each cardiac cycle? If that were to happen for instance with nor adrenaline then you might get a consequent bradycardia and peripheral vasodilatation

BURTON On the first point this red herring was originally raised by Hooker with regard to hæmodynamics It referred particularly to the kidney and it was said that if you perfused a kidney with a steady pres sure you got out much more renin than if you had a pulsatile flow I have always doubted this because it seemed very queer to me and I was delighted that it was disproved lately by two people independently As concerns the peripheral circulation I would think that if the swing

of blood pressure was enough to get off the long linear part of the pressure flow relation then it would make a difference but I doubt if it does in practice Your point about the receptors I think is a very good one indeed Obviously the mean pressure might be below the threshold of those receptors completely and never stimulate them *whereas the pulsatile pressure which has the same mean might stimulate* them at every systole

Dornhorst I am not quite sure that Dr Dawes has the situation the right way round With a noradrenaline infusion of this order the pulse pressure does not in fact change much The mean pressure increases and the systolic goes up much the same amount The heart rate slows and so the cardiac output as you would expect drops a little With adrenaline the mean pressure stays about the same and the pulse pressure widens round the mean pressure with an increase in heart rate *and an increase in output*

Dawes Why do you get a slowing of the heart with noradrenaline?

Dornhorst Almost certainly a sinus effect

Dawes Wouldn t that explain the phenomenon?

Dornhorst That is what I said.

Edholm The action of noradrenaline can be reasonably explained but the effect of adrenaline is much harder to understand

von Euler The after effect is remarkable It might possibly be explained by the assumption of a metabolite of some kind

Whelan The after *effect only becomes apparent* after the infusion stops and it only occurs after you have blocked the nerves or after you have completely sympathectomized the limb and you also see it in a completely denervated limb You do not see it if the sympathetic is acting In other words it would appear that normally after the infusion stops there is sympathetic activity which is bringing the flow back at a steady rate to the previous resting level If the sympathetic activity is absent you get this bounce

von Euler Then it is uninhibited so to speak

Whelan It looks as though the adrenaline is having several actions which are all super imposed one on the other—a local action i e an effect on the vessels an indirect action which could be due to lactic acid or something else and I also think there is stimulation of the sympathetic somewhere

Dornhorst One of the most puzzling phenomena I think is the early direct effect of adrenaline which is always quite transient but which will quite regularly reappear if the diffusion is stepped up It acts almost like a differentiating effect on the infusion rate but you never get any off effect—you never get any transient constriction of blood vessels on *cutting the infusion down*

Greenfield Does anybody know how long you would have to stop between infusions to get this odd initial spike the second or third time?

Whelan I do not think Allen (who tried this) stopped the infusion at all I think he switched from one infusion rate to the other without stopping

DORNHORST You see it even if you change to a different syringe which has a little more adrenaline in it

GREENFIELD But with the same dose does it come again?

DORNHORST It will certainly come again after the interruption if the machine stops for half a minute or so

EDHOLM How long intervals are required between intra arterial infusions to produce this effect?

WHELAN I do not know as I have not tried it

EDHOLM Professor Burton mentioned this morning that there was no evidence of vasodilatation in muscle vessels when blood flow was determined by the rate of clearance of radio active sodium However the time intervals between observations were relatively long and the dilatations might easily have been missed

BARCROFT Yes but I think the dose might have been at fault there In that case it was adrenaline injected locally into the muscle and the concentration at the site in the muscle must have been much bigger than when it was given intra arterially or intravenously When you give a very large dose intra arterially you get a constriction Perhaps there is not really quite as much discrepancy as would appear

BURTON My emphasis was I hope that this was *not* a real discrepancy because one method was measuring clearance and the other was measuring flow It is perfectly possible that adrenaline produces a change in the permeability of the tissue blood barrier and that this explains why the results were different

COOPER Have you observed this adrenaline effect in any cases of complete nerve lesions of the arm or avulsion of the brachial plexus?

WHELAN I have looked at a couple and the results have not been consistent enough for me to say very much about it When one starts measuring forearm flow it is lower in the denervated arm than in the control then it gradually rises to a fairly steady plateau flow The adrenaline response depends on when you give the adrenaline If you give it in the early stages you get a response which appears to be very much the same as normal In the stage when the denervated limb flow is very high we have seen in several cases a sharp fall in flow Whether there is a transient increase in flow I do not care to say on the small amount of data which we have

BURTON May I ask if the subjects feel anything when you change from saline to adrenaline?

WHELAN Oh yes

BURTON Could not this be the whole explanation of that big peak a fair amount of psychic reflex?

WHELAN The subjects tell you that they get a feeling of apprehension about the midriff and are usually very much aware of the increase of respiration in the beginning The increase in heart rate is also usually very appreciable to the subject That settles down and if you go on to say 10 micrograms a minute for an hour or more at the end of that time the subject really does not know if he is getting anything or not he has become accustomed to it However we had one subject who had had a late night and by the time we had got him into a plethys

mograph and the infusion going he was asleep We gave him 20 micrograms of adrenaline per minute and it did not wake him We did wake him up subsequently and repeated it and he said he had not been aware of anything happening when he was asleep I do not think that emotional changes could account for the large peak as the responses during sleep were just the same as when awake

DORNHORST Moreover one is quite unaware of it when the adrenaline goes in intra arterially and you still get this transient rise

EDHOLM An effect can be obtained on muscle blood flow using smaller doses which even intravenously do not produce any feelings of apprehension or consciousness of cardiac action

WHELAN At 5 micrograms per minute or under I think most people would not be aware of anything happening at all

BURTON I am very puzzled about this whole peak this is a continuous infusion with a fixed quantity of adrenaline What is the nature of this adaptive process by which the flow which went up suddenly comes down again? This to me is one of the most interesting things in the whole experiment We are accustomed to brief effects with adrenaline when injected in doses but not to this sort of thing when infused steadily

HERTZMAN Have you tried these experiments with the subject breathing 100 per cent oxygen?

WHELAN No

EDHOLM I think we can rule out apprehension as an important factor in the vasodilatation It is still difficult to understand what vessels are involved perhaps we can get some help by studying the architecture of the vascular system Dr Weddell can you provide a scheme which would explain this effect?

WEDDELL Not in a completely denervated limb

EDHOLM *Another point worth mentioning is that the bone blood* flow is probably diminished during adrenaline infusion there is no evidence of vasodilatation in the bone vessels

WHITNEY Do you know if this effect is accompanied by a change in the volume of blood in the veins? Is there any sort of venous constriction?

WHELAN It is accompanied by an increase in the volume of the fore arm as a whole but whether that is on the venous side or not I do not care to say not after this morning s discussion

HERTZMAN Have you had an opportunity to observe the sub cutaneous veins in these experiments to see whether they are engorged or whether they are constricted?

WHELAN No with plethysmographs on the limbs it is not easy to see what is happening to the veins

BURCH We have watched the veins of the skin and have observed them *constrict following intravenous admini tration of adrenaline*

BARCROFT You notice that very markedly in the leg It would be so convenient if you could do these infusions in the ankle and then have both arms for arm experiments But it is unfortunately impo sible to do that because as a rule all the leg veins constrict so tightly that you cannot infuse adrenaline through them

There is one point I might add here on a more general ground The intra arterial work which Dr Whelan has described shows that neither adrenaline nor noradrenaline is capable of dilating the muscle vessels directly That is of course apart from the short initial effect This is interesting when one thinks of Cannon s theory of the action of adrenaline According to Cannon adrenaline should help to bring more blood to the active muscle fibres by opening their vessels in exercise But in fact there does not seem to be any evidence that either adrenaline or noradrenaline has any such local action

ASMUSSEN Could it not be that the initial spike was an effect on the arteries and arterioles and the delayed effect was on the capillaries? The first effect could be checked by the blood pressure regulation and that is why it is so transient the later response would be a dilatation of the capillaries

WHELAN If the dilatation were a direct effect of adrenaline on the capillaries one would expect to see it during the intra arterial infusion One does not get any dilatation on intra arterial infusion

ASMUSSEN I was thinking of a lactic acid effect on the capillaries

DAWES Can the initial spike followed by a delayed effect be seen in experimental animals?

BARCROFT The only experiments I know showing the initial transient effect in animals are those of Clark s in which he described a dilatation followed by constriction But one difficulty is that very few animal experiments have been done with continuous infusion and the initial effect is then difficult to separate from the total effect

HERTZMAN I think something similar to this was done by Harry Hines on the femoral artery I cannot recall details of the data but he did infuse adrenaline steadily into both arteries of normal and denervated legs

BARCROFT Yes that is quite right but I do not remember the details either

BURTON Do you suppose it is possible that the amino oxidase takes two minutes to get to work on the adrenaline and this is why the spike comes down so quickly?

DORNHORST I thought the most plausible scheme was that the dilatation depended on the concentration gradient across some membrane which would disappear when equilibrium was reached it would reappear with a rise in infusion rate You would however expect an off effect coming down

EDHOLM It is surprising how rapidly adrenaline appears to be destroyed at the periphery If adrenaline is injected intra arterially a large dose has to be given before there is any increase in heart rate Can Professor von Euler tell us about the mechanism?

VON EULER I suppose some is being filtered out and some is being destroyed Lund in Copenhagen did some quite extensive experiments on the destruction of injected or infused adrenaline and noradrenaline in fairly large amounts I think he found that the liver inactivated these substances very rapidly and effectively as noted previously for adrenaline

EDHOLM What surprises me is that adrenaline must be destroyed in the muscles because intra arterial injection in the femoral artery does not cause any systemic effect

VON EULER I think Lund found in the rabbit that destruction in the muscles was due mostly to filtering out in the capillaries and subsequent enzymatic inactivation

DAWES I can give you some figures on this point If you inject adrenaline into the portal vein about one fifth reaches the general circulation as judged by the subsequent rise in blood pressure This proportion is much increased by simultaneous injection of pentamidine which reduces destruction in the liver If you inject adrenaline into the femoral artery only about one tenth passes through The best comment on this was by Elliott in 1903 or 1904 He said that adrenaline disappears in the tissues which it excites

VON EULER I think in regard to the amidines that they are very potent amine oxidase inhibitors

DAWES Yet the same phenomenon may be observed in the liver with sympathomimetic amines which because they have an alpha methyl group are not destroyed by amine oxidase Moreover there are certain of the amidines which are poor inhibitors of amine oxidase and yet prevent adrenaline destruction in the liver I do not think we yet know how adrenaline is destroyed in the liver

BURTON Many of you must be aware of the recent work in measuring the amine oxidases in peripheral arteries and so on It is coming to something very interesting isn t it? I was wondering how long it will be before someone has the courage in the human to infuse with a little ephedrine first which by competitive inhibition most effectively knocks out these amine oxidases then your adrenaline effect should be very marked indeed

VON EULER Propamidine is certainly very active at least in raising the content of the catechols in the organs We injected propamidine intramuscularly in the cat and it did not seem to have any effect on the animal itself we gave about 20 mg/kilogram

DAWES This must be a very complicated situation because propamidine also liberates histamine

VON EULER You could stop the histamine actions by giving some anti histamine

ASMUSSEN Would adrenaline disappear from the arteries if you infused it continuously for several minutes or does that only happen with a single dose?

DAWES Yes I gave both into the femoral artery of the cat The circulation actually stops and takes a long time to recover As Elliott said adrenaline has excited the tissues and has disappeared in the process We always talk about adrenaline being destroyed by some mystic process but if it causes smooth muscle to contract that is fair evidence that it is acting on some receptor and presumably being destroyed in the reaction

EDHOLM On the other hand with continuous intra arterial infusion the muscle blood flow increases abruptly and then declines approxi

mately to the control level although adrenaline continues to be infused Is there any excitation of receptors at that stage?

DAWES Are we talking about the cat or man?

EDHOLM Man at this stage

DAWES I was only talking about the cat It depends on the tissues excited You said you got a constriction but it is a vasodilatation isn t it?

EDHOLM The vasodilatation is transient although the infusion is continuous The curious part appears to be the stage following the vasodilatation

DAWES But is it so curious? The striking thing in the cat is the vasoconstriction in the hind limb When the muscles are first exposed to a relatively low concentration of adrenaline you get vasodilatation as the concentration builds up you get vasoconstriction

DORNHORST I think the evidence is against that isn t it? You get this effect when using adrenaline at 1/400th gamma a minute intra arterially up to about ½ gamma or so

GREENFIELD Has enough adrenaline been put into an artery that you might reasonably expect it to alter the heart rate when it gets round? I am thinking for instance of amounts of 3 or 1 gamma You would expect that there would have been some change

EDHOLM Is there in fact none?

BARCROFT Well there is no change in general arterial blood pressure

ASMUSSEN But immediately after the injection? I mean after waiting ten seconds or so

BARCROFT I do not think it has been mentioned—we have tried that

ASMUSSEN If that happened it would explain the pulse increase later on

BARCROFT But with infusions of 3 gamma if you take the blood pressure at quarter minute intervals with the ordinary arm method there is no change

DORNHORST I have noticed that if you are giving an intravenous infusion and measuring the brachial artery pressure and the forearm blood flow the brachial artery pressure starts to drop before the flow increase starts in the forearm Presumably though it has already started in the nearer part of the muscles and so the total peripheral resistance is falling but that incidentally shows that there is not a direct blood pressure effect The blood pressure is low by the time this starts

BURTON The infusion is done through a small catheter put into the artery isn t it?

WHELAN No the intra arterial is done by a small needle

BURTON But the blood is flowing past the needle and diluting the adrenaline you are putting in? Why isn t this straight cybernetics? Initially the flow was fairly low in the muscle and so there is a high concentration of adrenaline presented to it with a violent effect on the receptors (dilatation) but as soon as dilatation occurs the blood flow increases so now the receptors are receiving a much lower concentration of adrenaline

WHELAN But how does it go up again once it comes down?

BURTON It reaches a steady state between the two It would not be a non oscillatory system but would have this initial kick What I mean is that if it were an oscillatory system in cybernetics would it not re bound?

DORNHORST I do not think you can have that simply on concentration level It would have to have an integration in the loop somewhere (if you are going to talk of cybernetics) if you are going to come down to the original baseline Otherwise there must be a continuing error to provide the continuing stimulus

BURTON Yes but it is only a millimetre or two

DORNHORST No I don t think that will do!

BURTON It was a good attempt! It must be a factor of some importance in the problem mustn t it?

GREENFIELD I think there is an answer to that one If you infuse things like histamine at a steady rate intra arterially which might cybernetically do this in fact they do not do it The blood flow stays up

AHMAD In your case of hyperthyroidism it was seen that adrenaline had a marked effect It may be that the effect of adrenaline like thyroid hormone is also on the metabolic processes It is possible that both hormones act synergistically and the effect on blood flow is enhanced

WHELAN That is the only case I have done and I cannot say that the response was outside the limits of normal

HOWARD Dr Dornhorst raised a point that if this were a barrier effect you would expect there would be an off spike Have you any comment about the drop in flow which you get at the end of an infusion?

WHELAN At the end of intravenous infusion you get a steady fall off in flow from the sustained increase right down to the base line level The time varies but it takes about five seven or ten minutes before it is back to a steady resting level There is no off effect

HOWARD One or two of your records showed quite a sharp downward spike immediately after the infusion was stopped

WHELAN They were nerve blocks Following nerve block or in the sympathectomized forearm you get an initial sharp downward fall followed by this transitory after dilatation You do not get it intra arterially and you do not get it in the normal limb with intravenous infusion

DAWES I think the phenomenon which we have here is part of a general pattern I remember seeing this kind of thing in the stomach when John Vane was giving slow infusions of histamine either intra venously or intra arterially There is at first a great increase of blood flow through the stomach this increase becomes less after a short while and you reach a steady state with an increased blood flow but not nearly so great as that seen initially In fact you have a spike effect and a return towards normal

SHEPHERD We have been giving intra arterial histamine and adenosine triphosphate into the brachial artery and measuring the forearm blood flow With these drugs particularly with small doses we do occasionally see a transient increase in flow followed by a slight drop

to a steady rate of increased flow With larger doses the flows tend to increase to a sustained level without a preceding spike In any records where a spike is present the decrease in flow to the sustained level which follows is never as marked as with adrenaline

DAWES Yes I would not suggest that the fall in these histamine infusions was as great as this

BURTON I am delighted to see that after a little reflection Dr Dawes is coming round to the cybernetic possibilities If you perfuse the rabbit ear with Ringer containing a constant concentration of adrenaline this is what happens when you start the infusion of adrenaline instead of plain Ringer the flow diminishes right down almost to zero and after about a minute up it comes again It will go on doing this repetitively This is explained by the destruction of adrenaline the vessels close down and the enzyme gets to work the adrenaline is destroyed and the vessels open again get some more adrenaline and constrict once more Now I suggest that when in addition you have the diluting effect at the needle of the blood going by then some such explanation as this should be thought of The dilution effect the oscillatory possibility in such a system must definitely play an important part in this phenomenon of a spike

SHEPHERD If acetylcholine which is very rapidly destroyed in the body is infused into the brachial artery at a constant rate and the forearm blood flow measured thus circulatory oscillation does not occur The flow increases to a plateau which is sustained as long as the intra arterial infusion is continued On your hypothesis one might expect these oscillations to occur with acetylcholine

HERTZMAN Much of this motor activity that one sees occurs at high levels of blood flow and I do not believe that Dr Burton s explanation could apply in such cases

BURTON You have to admit that if the blood flow was increased four fold during that spike that means that the initial concentration of adrenaline which reached the tissues was four times as great as it is when you get to the top therefore you would expect a falling off to follow

HERTZMAN Not with an intravenous infusion It would be the other way round because suddenly your concentration would rise with the increased rate of delivery

BURCH Do you think the central nervous system has anything to do with the phenomenon of dilatation from adrenaline?

WHELAN No Because if you cut off the central nervous system either by blocking the nerves or by sympathectomizing the limb or by denervation you will get the same kind of response

BURCH Was the change equal quantitatively?

WHELAN Yes With the nerve blocks for instance the level of flow in the beginning is higher on the blocked side but response above that resting level is the same as in the normal limb The whole response is just pushed up In the sympathectomized cases where the flows were approximately the same you get the response on the two sides

CHANGES IN PERIPHERAL CIRCULATION* WITH EXPOSURE TO COLD

LOREN D CARLSON

Introduction

MILITARY operations as well as the rapid changes in travel facilities have given rise to an increasing interest in the mechanisms of adaptation in man to extremes of environmental temperature It is a common statement that evidence of adaptation to cold in man is lacking However in the light of recent experimental evidence to be presented in part in this communication certain adaptive mechanisms can now be described Most studies particularly on circulation are made on subjects acutely exposed to cold but it is emphasized that this discussion describes effects of continued or intermittent exposure over long periods of time The evidence that peripheral circulation is changed with adaptation to cold is derived from the analysis of skin temperature measurements plethysmograph studies resistance of extremities to frostbite and function of the extremities In the course of the discussion a tentative hypothesis concerning adaptation to cold will be presented

Skin Temperature Measurements

The observations of Balke *et al* (Balke Cremer Kramer and Reichel 1944) will serve to introduce the results of skin temperature measurements In studies on seven subjects living twenty one days in tents skin temperatures were determined daily The results on two subjects are shown in Fig 1

*The work reported here was supported in part by a contract between the University of Washington and the Alaskan Air Command Arctic Aeromedical Laboratory Ladd Air Force Base Fairbanks Alaska

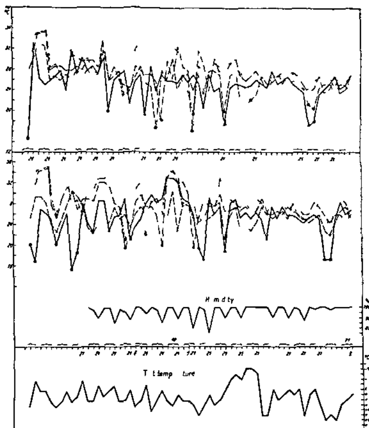


FIG 1 Skin temperatures of two subjects while camping out

- Toe temperature
- Knee temperature
- Back temperature
- Abdomen temperature
- ● Feeling cold
- ○ Feeling very cold

Relative humidity in per cent (upper right scale)
Tent temperature (lower right scale)

Balke *et al* (1944)

The tent temperature is shown in the lower portion of the figure The significant finding is that the rather large difference between trunk temperature and extremity temperature diminishes with time in the cold the extremity temperature tending to rise the trunk temperature falling slightly

Carlson *et al* (Carlson Young Burns and Quinton 1951) in a study on groups of individuals classified as adapted and

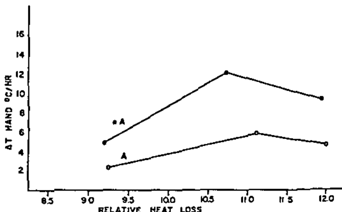


FIG 2 Change in hand temperature in degrees centigrade as related to heat loss from the body through a thermal gradient suit Subjects classified as adapted to cold though usually starting with higher hand temperatures show less drop in hand temperature Ordinate drop in hand temperature C per hour Abscissa relative heat loss A adapted nA unadapted Carlson *et al* (1951)

unadapted on the basis of the extent of their exposure to cold reported that the adapted individual when compared to the unadapted shows higher initial hand temperatures and less drop in hand temperature during standard exposure periods of one hour (Fig 2) In a later study Carlson *et al* (Carlson Burns Holmes and Webb 1953) followed five individuals during exposure to cold eighteen hours per day for fourteen days During the first days of exposure hand temperature during a standard one hour exposure fell rapidly

to freezing temperatures then fluctuated with time In the final days of the exposure the hand skin temperature showed a slower initial fall to approximately 10 C and the cycling or alternating rise and fall in temperature lessened in amplitude Some representative data are shown in Fig 3 The upper curves are experiments on the same subject at the same temperature on the second and twelfth day of exposure The lower curves are from a well adapted infantryman The effect of an increased negative heat load is shown at the right of the figure These measurements of skin temperature together with measurements of deep muscle temperatures confirm an hypothesis formulated by Carlson *et al* (1951) concerning adaptation in man Readjustments in circulation play an important role in this hypothesis and a brief description may be given here This hypothesis concerning the mechanism of adaptation to cold was derived from an analysis of simultaneous measurements of rectal and skin temperatures oxygen consumption and calorimetry by a thermal gradient principle Average temperature of the skin over the body was used as the independent variable since it is one of the body s signals for response to cold Compared at the same average skin temperature the adapted person produced less metabolic heat (as determined by oxygen consumption) Metabolism supplies less of the total heat lost (direct calorimetry) in the adapted than in the unadapted individual The extent to which cooling of the body tissues supplied heat was calculated from skin temperature changes The adapted person exhibits a definite tendency to donate the largest portion of his body to supplying heat Considering the assumptions made and the limited nature of the experimental data this hypothesis must be regarded as tentative When considered with Wyndham s (1951) description of adaptation to high temperatures the participation of core and shell in response to temperature stress becomes a continuum with temperature Namely, in low temperatures the core tends to diminish or withdraw in severe cold and at high temperature the core tends to expand to the surface in severe heat in the former case there

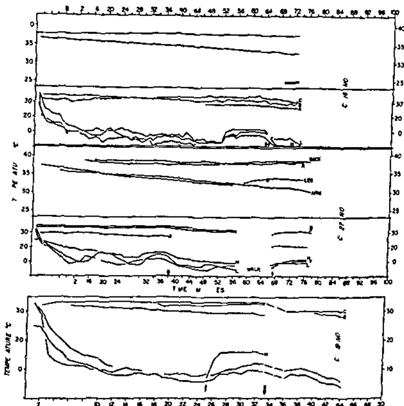


FIG 3 Skin temperatures recorded during exposure to outside air subject standing At one minute on each graph one hand was ungloved and exposed with only the rayon glove in which thermo couples were installed covering the hand At the arrow the glove assembly was put on At the double arrow the outer jacket and gloves were removed otherwise the clothing was kept the same Subject C arrived in Alaska on 15 November and lived outdoors during a 14 day test Subject Co was an enlisted man who had been on extensive field training prior to the test Skin areas sampled by thermocouples are indicated as H back of hand F forefinger tip L little finger tip C chest A forearm B back L lower leg

R indicates rectal temperature Deep thermocouples are indicated as back leg arm Mean temperature during the experiments C 16 and C 27 was −15 C and during experiment Co 10 was −16 C Solid bar denotes shivering

Carlson *et al* (1953)

is effectively more storage of heat in the body for combating cold stress in the latter case less storage of heat in the body to give an additional avenue of combating heat stress

Plethysmograph Studies

Carlson *et al* (1951) also obtained finger plethysmograph records in their subjects No measurements on blood flow

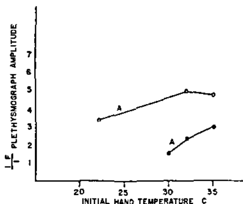


FIG 4 Finger plethysmograph amplitude change as related to initial hand tempe atures in subjects classif ed as adapted (a) and unadapted (nA) Individual values grouped and aver aged Ordinate shows change in plethysmograph ampl tudes as initial minus final pul e ampl tude divided by nitial amplitude Initial hand temperature s the a erage of fi e thermocouples on each hand

Carlson *et al* (1951)

were made These workers noted that there was less reduction in the amplitude of the pulse in the adapted person (Fig 4) Brown and Page (1952) presented striking evidence in their comparison of hand blood flow in the Eskimo (22 males on Southampton Island) with a control group (37 young men in Kingston Ontario) The data in Table I compare the two groups with respect to hand blood flow and hand temperature in a room at 20 C Note that though the blood flow is nearly

Table I

AVERAGE HAND BLOOD FLOW AND SKIN TEMPERATURE IN ESKIMO AND CONTROL GROUP IN ROOM AIR AT 20 C

(Brown and Page 19 ?)

	HAND BLOOD FLOW			H ND TEMPERATURE		
	No of subj	No of obser	Hand blood flow* ± S E	No of subj	No of observations of hand	Temp of hand in C
Control group	5	122	4 7±0 19	5	611	3- 8
Eskimo	6	148	8 0±0 43	6	~50	33 8

*In ml /100 ml of tissue/minute

double there is only a degree of difference in hand temperature The average hand blood flow at various hand water bath temperatures is shown in Fig 5 At any given water bath temperature the hand blood flow of the Eskimo is greater

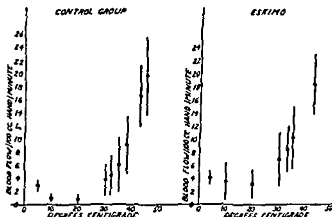


FIG 5 Average hand blood flow at various hand water bath temperatures in the Eskimo and the control group with standard deviations Each point is the mean value of all hand blood flow measurements made at that particular water bath temperature over a two hour period except in the case of the control group at . C when the period was 1½ hours

Brown and Page (19.?)

The results of experiments on skin temperature and blood flow are consistent with and offer explanation for the results of studies on resistance to frostbite and hand function studies

Resistance to Frostbite

The data reported by Blair *et al* (Blair Dimitroff and Hingeley 1951) from animal studies are illustrative of the evidence Groups of six rabbits and twelve rats were con ditioned to moderate cold exposure for a seven week period the rabbits at −29 C twenty hours of each day the rats at −7 C sixteen hours of each day At the end of the con ditioning period these animals along with similar control groups were exposed to severe cold the rabbits to −45 C for eight hours the rats to −15 C for five hours The cold conditioned animals without exception tolerated the period of exposure to severe cold without adverse effect neither hypothermia nor cold injury occurred All control animals suffered progressive hypothermia and second and third degree frostbite It seems necessary to conclude that these animals maintained their extremities above freezing by circulation It may be argued that the cold conditioned animals had an increased heat production and (or) an increased insulation and these factors certainly contribute However in regard to this argument it should be noted that Sellers *et al* (Sellers Reichman Thomas and You 1951) report little difference in heat output of animals as measured by oxygen consumption during initial cold exposure and after weeks of cold exposure Carlson and Cottle (1953) report similar findings by direct calorimetry and these workers note that the extremity tem peratures in animals conditioned to 5 C are higher than those of animals initially exposed Further in the studies on man Carlson *et al* (1951) found no distinguishable difference in heat output of adapted and unadapted persons as measured by direct calorimetry at different environmental temperatures

Hand Function Studies

The final evidence evolves from the studies of Mackworth (1952) concerned with finger numbness The test was a kind

of two point threshold The experimental apparatus consisted of a V test device which measured the size of the smallest gap between two sharp wooden edges which the subject could just

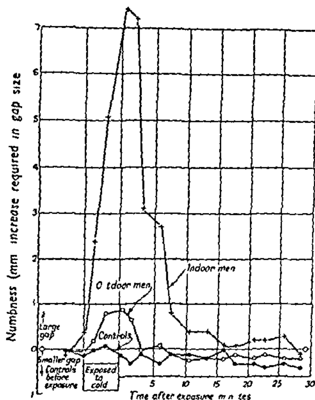


FIG 6 Numbness trends from indoor and outdoor men—exposure to slight win l

Mackworth (19.2)

detect by touch alone when pressing with the tip of his fore finger The index of numbness for each subject is given in millimetres increase in the physical gap size required to preserve the tactile impression of the gap despite any numbness A marked difference in the numbness index between men accustomed to being indoors and those to being outdoors

during the winter at Fort Churchill Canada is illustrated in Fig 6 The outdoor men had a less marked fall in skin temperature The marked differences suggested the further test shown in Fig 7 which illustrates the day by day trends in numbness index during acclimatization (exposure of two hours per day to −15 C)

These studies of resistance to frostbite and hand function

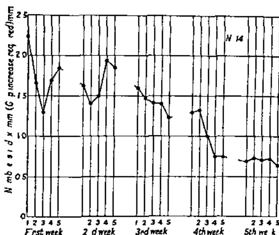


FIG 7 Day by day trends in numbness index during period of exposure to −15 two hours daily

Mackworth (1953)

suggest that there is less marked vasoconstriction with adaptation to cold

Possible Mechanisms

One immediately recalls the report of Grant (1929 31) and Grant and Bland (1929 31) that the areas under discussion have many arteriovenous anastomoses in fact they are the chief areas where arteriovenous anastomoses are found The regulation of blood flow and the extent to which these anastomoses function are a matter of conjecture as little data

exist It might be suggested by way of speculation that an increased rate of blood flow through the hand occurs by way of these anastomoses

Des Marais and Dugal (1950 1951) studied the adrenaline sensitivity of the vessels of the meso appendix of rats which had been exposed to cold for varying times Their conclusions are based on the assumption that hypersensitivity of the vessels to adrenaline corresponds to a state of vasoconstriction

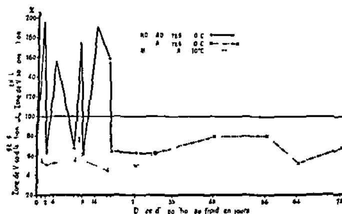


FIG 8 Sensitivity to adrenaline as measured by the method of Chambers and Zweifach during exposure to cold Ordinate sensitivity to adrenaline showing zone of vasodilatation and zone of vasoconstriction Abscissa duration of exposure to cold Des Marais and Dugal (1951)

a diminution of sensitivity is generally recognized as a preparation where vasodilatation is apparent Rats exposed to 0 C showed initially alternate phases of vasodilatation and vasoconstriction by this criterion and with complete adaptation established a new rate of peripheral circulation which the authors call light vasodilatation (Fig 8) While exposure to cold gradually increases the adrenal content of both adrenaline and noradrenaline until adaptation is reached these authors believe that the modifications of circulation are independent of the secretion of the adrenal medulla In their

opinion the phenomenon is due to a modification of the sensitivity of the blood vessels to the action of vasomotor amines possibly by adrenal cortical secretions certain lipids or other substances The observations of Grant (1929 31) concerning the effects of adrenaline on the arteriovenous anastomoses and the conclusions of Grant and Bland (1929 31) concerning the function of these vessels during acute exposure to cold need to be correlated with the observations of Des Marais and Dugal (1951)

Greenfield and Shepherd (1950) interpreted their observation of the lack of correspondence between plethysmograph data and calorimetry data as an indication of lack of capacity vessels in the cold finger and deduced that the finger plethysmograph did not give reliable results below 30 C These studies should be extended to cold adapted subjects Carlson and Rushmer (1953) observed the rate of rise of venous pressure in the hand with venous occlusion at the wrist in unadapted persons at environmental temperatures from 25 C to 10 C The rapid rise of venous pressure which might be expected from the observations cited was not apparent in our data

Conclusion

It seems that the evidence though of circumstantial nature indicates that a readjustment in circulation is involved in adaptation to cold The adapted person tends to keep extremities warmer This allows the adapted person to endure the exposure to cold with less discomfort and loss in manipulatory efficiency Mechanisms for this change may be postulated but the exact description awaits experimental proof

Maintenance of the extremities at relatively higher temperatures gives rise to greater heat loss The area involved is not great There is evidence of slight changes in trunk temperature so that little increase in total heat loss occurs

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[Discussion of this paper was postponed until after the paper by Prof Greenfield —Ed]

THE RESPONSE TO COLD IN THE RANGE 0-10 C

A D M GREENFIELD

THE experiments which I propose to discuss to day have been carried out in collaboration with Dr Shepherd and Dr Whelan both of whom are members of this Symposium

We set out to make a quantitative study of the response to cold of the digital blood vessels This had been described qualitatively by Lewis (1930) who based his observations largely on measurements of the temperature of a thermo electric junction in contact with the skin and covered over with layers of adhesive plaster He described the initial vasoconstriction followed by recurrent periods of vaso dilatation which we and all subsequent workers have con firmed We started our observations using digital plethysmo graphs containing stirred water and attempted to measure flow by venous occlusion We quickly found (Greenfield and Shepherd 1950) however that the relatively small capacity of the digital vessels which makes this method difficult to apply and slightly suspect even at ordinary temperatures was conspicuous at low temperatures and we had no confidence in our ability to draw tangents to the inflow curves or other wise interpret them It was clear however that the pulse waves were first greatly reduced for a few minutes and later became unusually large As far as it went this confirmed Lewis but it failed to provide us with quantitative flow measurements

We turned therefore to calorimetry which was first employed by Stewart (1911) only six years after Brodie and Russell (1905) had devised venous occlusion plethysmography The finger tip is a particularly favourable site for calorimetry It has a large surface to volume ratio which permits good heat exchange and minimizes the lag of the calorimetric response

behind blood flow changes in the finger The blood returning from one finger tip is a small fraction of that from the whole hand and so even if the finger tip blood is severely cooled, it does not lower the mixed venous blood temperature very much and so has a relatively slight effect in pre cooling arriving arterial blood (Bazett *et al* 1948) Concern about the degree of pre cooling of arterial blood is in any case much less at a calorimeter temperature of below 10 C than at higher temperatures A Dewar flask of about 1 litre capacity immersed in ice cold water provides a calorimeter which in the 0 6 C range gains heat from the vasodilated immersed finger tip about ten times as fast as from all other sources The warming correction is therefore quite small compared with the quantity of heat to be measured The finger/calorimeter system has a reasonably short lag following sudden arrest of the circulation more than half of the heat stored in the finger is given up in the first minute The system is extremely simple to set up and to operate No drawing of tangents is required and although transient changes may escape notice the calorimeter has the advantage of automatically integrating the fluctuating heat loss

We have adopted immersion in a water bath at 29 C for ten minutes as a standard treatment before transfer to the cold calorimeter During the first five to ten minutes of immersion the heat loss from a finger to the calorimeter is just the same whether or not the circulation is arrested by a pneumatic cuff at the moment of entry into the calorimeter Evidently the effect of immersion is initially to produce an intense vasoconstriction which arrests the circulation as promptly and as completely as a pneumatic cuff inflated above arterial pressure After five to ten minutes however heat loss from the finger with a free circulation begins to rise abruptly and reaches a figure of about 2000 cal per 100 ml of immersed finger tip per minute As it is found that no appreciable portion of this heat is conducted down the finger from non immersed parts or derived from tissue metabolism it must come from circulating blood As the blood cannot

arrive above central body temperature or leave below calorimeter temperature a heat clearance calculation shows that blood flow through the finger tip must be at least 60 ml per 100 ml per minute Since the average internal temperature of the finger tip is about 25–30 C at the height of cold vaso dilatation while immersed in water at about 2 C (Greenfield Shepherd and Whelan 1950) it is probable that the temperature of the departing venous blood is also about 25 30 C and on this basis it becomes clear that the blood flow through the finger tip is of the same order as is obtainable by other vaso dilating procedures Thus after immersion we have complete vasoconstriction for five to ten minutes followed by rapid and full vasodilatation The subsequent irregular episodes of constriction which punctuate the dilatation may or may not be complete and may or may not be very sudden in onset (Greenfield Shepherd and Whelan 1951a)

The vasodilator response was found by Lewis (1930) to be present in sympathectomized limbs and in acutely denervated limbs but not in chronically denervated limbs On this was based the suggestion that the response is due to a somatic nerve axon reflex Our own observations on denervated fingers in the main confirm Lewis s findings when the tests are made under similar conditions We have been struck many times however by the way in which the recent temperature and other conditions of vessels can influence their response and behaviour Responses do not depend solely on the conditions at the time of the observations We therefore investigated (Greenfield Shepherd and Whelan 1951b) the effect of various degrees of preliminary warming of the chronically denervated finger on the subsequent response to cold It was found that after immersion for twenty minutes at 41–42°C the denervated finger showed a response similar to though smaller than that of a normal control finger This suggested that the axon reflex or at any rate an axon reflex pathway depending on the integrity of the somatic nerves was not essential although it was helpful to the cold response

These observations are subject however to an uncertainty

Although sensation and sympathetic control were completely lacking in the fingers tested some axon reflex pathways may have survived These may have been in posterior root fibres or in the axons of peripheral autonomic ganglia the existence of which has recently been discussed by Hilton (1953) It is notoriously difficult to prove complete dener vation and we still lack histological evidence on previously tested limbs

These difficulties appear to be removed by observations on the response of the finger tip after infiltration with local anæsthetic This may be expected to block all varieties of nerves In these experiments (Greenfield, Shepherd and Whelan 1952) it was necessary to revert to surface tempera ture measurements over the pulp of the finger as it was not thought to be possible to infiltrate the whole of the finger tip including the nail bed with anæsthetic solution Care was taken to inject the anæsthetic in a way which was likely to reach all the nervous elements rather than to block the nerves at one point in their course In these experiments the vaso dilator response to cold was still seen These experiments suggest therefore that the response can be seen when all nervous elements are out of action

We have therefore turned our attention to a possible chemical mechanism We thought that if it could be shown that a substance was capable of advancing the time of the initial cold dilatation it would be a candidate for consideration as a possible mediator of the response Substances failing to do this could not however be excluded from consideration because we might have failed to deliver them in the right concentration to the right place We have been unable (Duff Greenfield Shepherd Thompson and Whelan 1953) to ad vance the time of onset of the initial cold vasodilatation by intra arterial injection or electrophoresis of amounts of histamine and acetylcholine capable of producing a large effect at normal temperatures But in all cases there is doubt as to whether, with the vessels in severe vasoconstriction at the time of administration the substances actually reached them

Thus we cannot on this evidence exclude histamine and acetylcholine

A rather more significant observation however is that the cold response is quite normal in a fully atropinised finger tip This suggests that acetylcholine is not involved

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DISCUSSION

HERTZMAN Did you compare the subject s topical sensation with the mean skin temperature of the body or at any rate your regional skin temperatures? Would there be any evidence in your data as to a possible thermosensory adaptation so that vasomotor reflexes (for instance in the finger) are less intense because of less stimulation of cold receptors?

CARLSON We have no complete data on this but our general impression is that it is most difficult to get people to wear the same insulation (the same clothing) during exposure after adaptation They find it uncomfortable and warm In general therefore I would say that after the adaptation the sensation would be one of warmness in the individual

EDHOLM Dr Pugh has carried out experiments on another aspect of cold acclimatization in a long distance swimmer who was able to tolerate very long periods of immersion in cold water His mean skin temperature in comfortable conditions was about 2 5 C lower than that of other normal individuals who had mean skin temperatures of 33 5 C. to 34 C This Channel swimmer had an extremely thick layer of subcutaneous fat two to three times greater than in other subjects studied

CARLSON Our earlier study would indicate that the mean skin temperature of the adapted person was *slightly lower than that of the*

unadapted Certainly the general observation on which we have no full data would be that they were less sensitive to cold They give responses of comfort when their skin temperature was actually the same or lower than that of the other people

HERTZMAN We had one student last summer with a very clear cut demonstration of a totally different thermal threshold in sweating response He was comfortable at a skin temperature at least a degree higher than his fellow subjects who were sweating profusely when he was sweating slightly However eventually when the thermal stress got high enough he delivered the same quantity of sweat as the good sweaters He just simply operated on a higher body heat constant He did not become uncomfortable until he also obtained high sweating rates

CARLSON I think thermal studies have pointed to this particular problem We should study the shivering response as well as the onset of vasoconstriction in the adapted and non adapted individual as physiological end points The subjective response should also be obtained

NIELSEN Were your experiments on human subjects made under basal conditions? What happened to their metabolism?

CARLSON They were not made under basal conditions but under what I suppose we should call standard condition They were made at the same time every morning after a standard breakfast and they were always made standing The comparisons that we have would indicate that the response over the hour period of the unadapted was that of a higher metabolism because of the shivering which we saw in these people but did not see in the others

NIELSEN The mean skin temperature of the adapted persons might then be expected to be lower than that of the unadapted The temperature of the hands and feet however was actually higher Therefore unless there was a compensating decrease in the temperature of other skin areas the body heat content must have diminished more rapidly in the adapted than in the unadapted

CARLSON Yes

BURTON I would like to congratulate Dr Carlson on a very masterly review of this whole subject to which I can add very little although I have been intensely interested in this subject and read everything I could for years I would point out however that there does remain a fundamental problem concerning the energetics of this matter Dr Carlson has thrown great light on the nature of this adaptive process in man and other people have done so in animals Adaptation apparently consists in keeping the peripheral tissues warmer and therefore produces a greater efficiency in the cold and a shift between the core and shell of the body As he pointed out this will only operate in the non steady state It cannot go on for ever and the fact is that in animals it has been shown (particularly by Blair and by Dugal and co-workers by Hart also on smaller animals) that if you expose these animals to longer periods of extreme cold they do not die they keep up the body temperature for hours whereas in the unacclimatized animals body

temperature falls and they do die. We are getting to a very difficult position because it seems to be apparent that after exposure for about an hour or so the heat production is not any higher, so we would predict a lower heat loss. It now turns out that the mean skin temperature, if anything, is the same or perhaps slightly lower by compensation between the trunk and periphery. But it is only slightly lower and the heat loss by direct calorimetry seems to be much the same. How then is it that these animals manage to survive? This is the great fundamental problem of energetics which I feel remains.

I have one more point while I am speaking and that is that I know this conference will be interested in a beautiful experiment recently which is in the press but not yet published by Dr Lawrence Irving who works in Alaska. He has taken a peripheral nerve from a dog not acclimatized to cold and measured the conduction in the peripheral nerve isolated in Ringer's solution. He lowered the temperature of the solution and found the point at which conduction was reversibly blocked by cold—I think it was at about 15° C. He then let the dog out of the lab into the cold just for one week, then took the nerve of the opposite leg and did the same experiment on it. He found that conduction persisted right down to about 9° C. This brings strikingly home the fact that there are these *tissue adaptations*—biochemical tissue adaptations which up to now we have been neglecting very much.

DORNHORST: Dr Burton, was the water loss large enough to account for the difference? It is quite conceivable that with exposure to cold there should be changes in the evaporation of water from the skin; do you think that is big enough to be a substantial saving?

BURTON: I think Dr Carlson would agree with me that there is very little hope of explaining this matter in that way, because in the cold, if the animal is not sweating (and he seldom is) there is only the insensible loss of water, that is a purely physical thing which is remarkably unchanged by dehydration, as Adolph showed years ago. I doubt, therefore, whether we have much hope of calling that in to explain the survival on long exposure.

VON EULER: Professor Carlson referred to some paper showing that adrenaline would be given off by the suprarenal during the cold. Is there really any good evidence for that? I am asking, because I think that the adrenergic vasomotor system would usually be sufficient to cope with the problems during cold. It might perhaps be of interest to see whether this emergency substance, i.e. adrenaline, is important in this respect—I suppose one could do experiments on an adrenalectomized animal or even on an adrenalectomized man, to see whether they would show the same type of reactions. Nowadays there are quite a number, aren't there, of adrenalectomized people who are kept up by a certain dose of cortisone and who could be used for this kind of experiment.

BURCH: I would like to make an observation concerning the problem of comfort and what might be called acclimatization. In adjusting our laboratory or climatic rooms for comfortable temperature in the winter we have to adjust the temperature a little lower than we do in the

summer For example we find that 73 75 F will be suitable for most people with little clothing lying in the bed in their cotton or nylon underwear and covered with a sheet In the summer we adjust the temperature to about 75 F Whether this is due to psychogenic factors or whether it is acclimatization I do not know

I should like to ask how much of the observed reaction is an expression *of injury and how much is acclimatization a normal physiological* response? Expressions of injury may be likely

WHITNEY Professor Greenfield have you repeated your calorimetric measurements daily on the same subject? I think you said that you obtained the maximum expected response on the first presentation Did you have any evidence of an increase in response on repetition of the experiment on the next day?

GREENFIELD If you repeat observations three or four times the response does not increase but we have never continued really long enough to be able to answer your question properly

WHITNEY *I am interested in this because in the response of the* hand flow to high temperatures I find that on the first day or two of acclimatization the hand blood flow only rises to a level of about 30 to 40 ml /100 ml /min After several days acclimatization in the same pattern of heat and work you find that the hand blood flow will rise to almost double that figure And yet the fact that the man may faint at the beginning of acclimatization rather implies that the maximum response would be brought into action I wonder if anyone has any idea as to how the maximum possible blood flow can be increased in the hand—is it a matter of opening up A V connections which are normally *closed down or is it the conversion of ordinary capillaries into something* more like A V connections?

GREENFIELD Is it possible that your subject who was under rather unpleasant conditions was perhaps apprehensive on the first days of your experiments?

WHITNEY I don t think so—that might work on the first day but on the second day they did not as a rule faint

EDHOLM Your subjects are being exposed daily and so are developing an acclimatization to heat There are many physiological changes associated with such acclimatization including an increase in blood volume which might be expected to modify the vasomotor response

WHITNEY Yes but how?

EDHOLM I don t know what the mechanism is

BURTON The finger blood flow work that Bazett and I did many years ago certainly does show that in the first week of exposure in a continuously warm room it does go up from say 80 ml /min/100 ml tis ue to fantastic values of say 130 There is a very marked change in the veins too But this after all is acclimatization to heat which is not the subject we were discussing

HERTZMAN I should like to discuss the vascular response in the fingers to cold based on some observations we made a decade ago with the skin pulse technique *I think it has some advantages over the conventional* flow methods in that time relations in the reactions can be defined

precisely As I recall the constriction to cold appeared simultaneously in the fingers and toes on the immersion of one finger only in the ice water however as the intensity of the constriction developed to a greater degree in the chilled finger I interpreted that to mean that the initial constriction was elicited by the vasomotor response on which a direct effect of cooling was subsequently superimposed In experiments on the sympathectomized extremity we still obtained the intense con strictions but they developed gradually Rapid dilatation appeared in the same manner in the sympathectomized finger as in the normal finger But there was this interesting fact about the rapid dilatation in the non denervated finger for some time during its development a vasomotor reflex could not be elicited in the chilled finger Usually the dilatation was brought to an end by some vasomotor reflex elicited by a deep breath or some noise when a repetition of the cycle would occur These cycles are apparently related to varying periods of vasomotor paralysis and of vasomotor activity The question comes to mind what is the actual temperature at which the vasomotor fibres become para lysed? The internal temperature of the finger must be much higher than at the surface

Another interesting item in these observations deals with the changes in the character and the form of the skin pulse At the time of active dilatation when the finger was hyperæmic the skin pulses were no longer triangular as in the normal finger but were markedly rounded the crest of the wave might come after the dichrotic wave in the control finger As the hyperæmia disappeared the rounded wave began gradually to become triangular in form again the skin pulse had its normal tri angular form We interpret this to mean that during the reactive phase there were reactions by arterio venous anastomoses and that the pulse wave followed a different pathway Yet the amplitudes of these pulses might not be markedly different throughout the whole period of reactive dilatation

GREENFIELD We can agree with Dr Hertzman about the ease with which you can precipitate vasoconstriction by things like taking a deep breath but *I think they are not the whole tale As Lewis originally* showed and we have frequently confirmed if you look at two fingers simultaneously in the cold although they begin to hunt together after a bit they hunt asynchronously so that they can evidently hunt without being tipped off by some alteration of general vasomotor tone In variably when we are looking at one finger we look at another one at 29 C and there does not appear to be any clear correlation over a long period of time between the behaviour of the one which is at 29 C and the one which is in the cold

HERTZMAN I doubt whether there is any real contradiction I have never seen the constriction in the chilled finger occur independently of the constriction in the control finger That the cycles do vary in different fingers is perfectly possible but the vasomotor reflexes bringing on constriction occur in other fingers simultaneously the cycles can vary but the basic mechanism would still be the same A vasomotor reflex initiates the constriction

GREENFIELD Could it possibly be the other way round? That as soon as the vessels constrict the finger gets cold and painful again and this leads to increased vasoconstriction tone elsewhere?

HERTZMAN No there are vasomotor reflexes which may be independent of pain The pain follows the vasoconstriction it does not precede it

SHEPHERD Constriction occurs of course just as easily in the completely denervated finger

HERTZMAN It has a totally different time course though The reduction in skin pulse amplitude is gradual in the denervated finger but abrupt in the normal finger

WHELAN But the hunting reaction still occurs in the denervated finger

HERTZMAN Yes but the abruptness of the changes is reduced

WHELAN Its onset cannot be a vasomotor reflex then can it?

HERTZMAN The onset of the rapid dilatation is not vasomotor

DORNHORST There is no contradiction surely If you have a system which tends to go in these spontaneous oscillations like Dr Burton's perfusion of the isolated ear it is quite easy to imagine it locked in by vasomotor constriction and triggering off spontaneous constriction I do not think one would need to postulate that the nerves in the fingertip were still conducting because I imagine vasoconstriction in the digital arteries even in the base of the finger might be quite enough to drop the local blood pressure and start off the spontaneous constriction

HERTZMAN The timing though is just the opposite In the digital artery constrictions follow the changes in temperature and the digital artery dilatations follow the changes in temperature

DORNHORST These are based on your pulse waves?

HERTZMAN Yes

DORNHORST I am not too sure you can interpret those unequivocally

HERTZMAN I agree but the fact that the correlation of time with the temperature changes is very good suggests that the skin pulse is indicating what is actually happening

FACTORS CONCERNED IN THE REGULATION OF SKIN BLOOD FLOW

D McK KERSLAKE and K E COOPER

EVIDENCE of vasoconstriction in remote skin areas in response to local application of cold was furnished by Brown Sequard and Tholozan in 1858 who found that immersion of one hand in iced water caused cooling of the opposite hand This phenomenon has been confirmed by other workers (Francois Franck 1876 Muller 1905 Stewart 1911 Sturup Bolton Williams and Carmichael 1935 Uprus Gaylor Williams and Carmichael 1935) The response was examined more fully by Pickering (1932) who showed that immersion of one hand and forearm in cold water with the circulation occluded caused a transient vasoconstriction in the opposite hand and that when the circulation was released there was a second lasting vasoconstriction It is possible to analyse the response to cooling the unoccluded limb into a short lived component due to nervous afferent stimulation and a slower component due to cool blood returning from the limb to the general circulation (Sturup Bolton *et al* 1935)

Similar factors have been shown to control the reflex vasodilatation which takes place in the hand and forearm on warming other skin areas (Winkler 1902 Gibbon and Landis 1932 Pickering 1932 Uprus Gaylor *et al* 1935 Uprus Gaylor and Carmichael 1936 Stewart 1911 Duthie and Mackay 1940 Kerslake and Cooper 1950 Cooper and Kerslake 1949) The regulation of deep body temperature could be effected by a mechanism sensitive only to this temperature but control would be more efficient and stable if information concerning the exchange of heat from the body to the environment were also used A system whereby a decrease

in skin temperature promoted vasoconstriction and *vice versa* would not be inherently stable and would have to depend on suitable rates of adaptation of the temperature sensitive endings It would thus be inoperative in the steady state and of doubtful value at other times The information which could most readily serve to stabilize the thermal responses of the body would be that concerning the rate of loss of heat from the skin surface This is itself directly related to the skin blood flow (Cooper Cross Greenfield Hamilton and Scarborough 1949) so that if an increase in skin heat flow caused a vasoconstriction a regulating mechanism would exist tending to stabilize heat loss The level at which heat loss was stabilized could be controlled by modification of the heat flow/blood flow relationship depending on the deep temperature

This view of the possible function of the cutaneous receptors responsible for the reflex control of blood flow is consistent with previous results if it is also supposed that the receptors do not distinguish the direction of the heat flow through the skin but only its magnitude Grayson (1949) has shown that at high environmental temperatures there may be a vaso constriction which lasts until the deep temperature has begun to rise The immersion of a limb in either cold or very hot water would be expected to cause reflex vasoconstriction, and if the circulation to the limb were occluded this vaso constriction would wear off as the rate of exchange of heat between the limb and water grew less Release of the circu lation would tend to re establish the previous rate of heat flow The observed fatigue of the constrictor reflex to cold could be explained on this basis and also the failure of many workers to observe reflex vasodilatation on heating limbs until the deep temperature had begun to rise

The work to be described in this paper was undertaken with these ideas in mind in order to investigate the nature of the thermal stimuli to which the nerve endings responsible for reflex control of the cutaneous circulation were sensitive

Methods

The subject was seated in a domestic bath with his right hand in a water filled plethysmograph arranged comfortably on a shelf across the inside of the bath The plethysmograph water was stirred and maintained at 35 C This temperature was chosen in order to minimise the loss or gain of heat by the hand The bath was filled with water up to the level of the subject s waist and maintained at this level by means of a pump which rapidly removed any excess water It was stirred by a second pump connected to a perforated tube running round the periphery of the bath under the water Supplies of hot and cold water were passed through flow regulating taps to a tube which terminated near the intake of the stirring pump In this way the bath temperature could be changed fairly rapidly and differences in temperature of the water in different parts of the bath were minimized Above his waist the subject wore the upper part of an inflatable exposure suit This was kept fully inflated by connection to a constant pressure source of air derived from the room air There was no deliberate circulation of air through the suit but this arrangement was found to be necessary in order to compensate for small losses of air changes in temperature and changes in the posture of the subject The suit included a hood covering the neck and scalp The subject s face was covered by a service gas mask from which the breathing tube had been removed This arrangement restricted the loss of heat from the face although a small amount of air movement was present and may have allowed some heat exchange The left hand was not covered by the exposure suit but was immersed in the bath water

It was hoped by these means to make the heat loss from the upper part of the body negligible but it was found necessary in addition to arrange that the ambient air temperature in the room was 38 C Humidity was not controlled but was fairly high because of the evaporation from the bath A check on the rate of heat loss from the trunk and arms was made by applying tellurium heat flow discs in various places

(Hatfield 1949) These were connected in series so as to give a mean estimate of the rate of heat loss This was found to be very small indeed

The heat flow through the immersed skin could not be measured directly An estimate of it was made by applying tellurium heat flow discs (Hatfield 1949) in various places on the skin of the abdomen buttocks and legs These again were connected in series and the total potential generated was measured Although the discs themselves are calibrated in absolute units of heat flow it is clear that the actual heat flow through the whole of the immersed skin will be greater than that registered by the discs because of the insulation they provide at the points where the measurements are made The heat flow readings can therefore only be taken as an index of the actual heat flow although it is probable that the readings would bear a roughly linear relation to the actual heat flow through the immersed skin The skin heat flow for each minute was expressed as the mean of the galvanometer readings at the beginning and end of the minute

A measurement of deep body temperature was also required For this purpose the rectum was regarded as unsuitable because of the considerable changes in temperature to be expected in the venous blood returning from the legs (Bazett Love Newton Eisenberg Day and Forster 1948) In the absence of any significant loss of heat from the upper part of the body it was considered that the mouth temperature could be used as a satisfactory index of the temperature of the blood going to the brain Accordingly mouth breathing was prohibited and the sublingual temperature was measured by means of a fine thermocouple of low heat capacity The mouth temperature for each minute was expressed as the mean of the temperatures read at the beginning and end of the minute

Hand blood flow was measured by means of the plethysmograph on the right hand The volume changes were recorded electrically (Cooper and Kerslake 1951) and the collecting cuff inflated to 60 mm Hg for 5 sec every 10 sec The six

inflows recorded each minute were averaged in order to obtain the mean blood flow for the minute concerned

The temperature of the immersed skin was assumed to be approximately equal to the temperature of the bath water The error involved is probably small since the range of temperatures concerned is large (25–45 C)

Results

The only measured variable under direct control was the bath temperature and when this was changing it was less uniform throughout the bath than when it was steady The experimental procedure was therefore to set the bath temperature at some value and to follow the changes in heat flow mouth temperature and blood flow When these had begun to stabilize the bath temperature was changed and the procedure repeated It was found difficult to obtain sustained high values for heat flow and as this was the quantity with which the experiment was primarily concerned the rapid changes in bath temperature were frequently made from one extreme to the other At the same time when the heat flow was large the rate of change of mouth temperature was also usually large (up to 0 5 C per min) Since there was probably a lag in the transmission of blood temperature changes to the mouth and also to whatever part of the brain is concerned with thermal regulation the readings at high heat flows are probably inaccurate in that they do not reflect the temperatures obtaining in the relevant parts of the brain at that time In addition the lag in the vasomotor response in the hand (15 sec for reflex dilatation to heat) (Kerslake and Cooper 1950) may introduce appreciable inaccuracy when mouth temperature or heat flow is changing rapidly

Two experiments of about 90 min duration have been performed in each of three subjects The results of each pair were pooled in order to obtain a maximum of data on each subject for analysis

Results were first plotted on a three dimensional graph with blood flow as ordinate heat flow as abcissa and mouth

temperature as the height of the point above the paper Points on either side of the zero heat flow line appeared roughly symmetrical, confirming the idea that the heat flow endings are unable to distinguish the direction of flow of heat For analysis therefore the direction of the heat flow was ignored and only the magnitude of the flow taken

A three factor statistical analysis of the results was first performed with blood flow as the dependent variable The partial correlations of this with mouth temperature heat flow and immersed skin (bath) temperature were determined and it was found in every case that the mouth temperature correlation was significant Blood flow was negatively correlated with heat flow but there was no significant correlation with bath temperature Results were therefore recalculated on the assumption that bath temperature was without direct effect on hand blood flow The equations which fit the observations best (assuming linear correlations in each case) are given below

D K $F = 20\,(T_m - 36\ 1) - 4\ 1\ H_s$
K C $F = 23\,(T_m - 36\ 0) - 4\ 9\ H$
R M $F = 26\,(T_m - 36\ 3) - 5\ 1\ H_s$

Hand blood flow F is in ml per 100 ml hand per minute mouth temperature, T_m is in degrees Centigrade and the heat flow through the immersed skin H_s is in arbitrary units The differences between subjects are small and without statistical significance

These results are consistent with the mechanism for control of heat loss suggested earlier in this paper The data are too variable to permit a more precise examination of the nature of the relationship between blood flow and the two controlling factors investigated Clearly there will be an upper limit for blood flow, and in any case it seems improbable that the relationship between afferent stimulation and blood flow as controlled by efferent constrictor or dilator tone should be linear

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[Discussion of this paper was postponed until after the paper by Prof Barcroft and Dr Dornhorst —Ed]

BLOOD FLOW RESPONSE TO TEMPERATURE AND OTHER FACTORS

H BARCROFT and A C DORNHORST

THE first part of this paper describes some experiments by Aziz Ahmad (1953) on the effect of alterations of local temperature on the blood flow in the hands The subject of these experiments was a girl aged 17 Both her hands had been sympathectomized for excessive sweating by the extirpation of the 2nd 3rd 4th and 5th thoracic sympathetic ganglia

On the tenth day after operation the hands were placed in venous occlusion plethysmographs and a body warming test was performed which showed that both had been completely sympathectomized While the hands were still in the plethysmographs it occurred to Aziz Ahmad that it would be interesting to try the effect of increasing the temperature of the water from 32 to 41 C He was surprised to see that the hand blood flow decreased

The experiment shown in Fig 1 was done on the thirty seventh day At the beginning the temperature of the water in the plethysmographs was maintained at the usual level of 32–33 C After the body had been heated for forty minutes the temperature of the water surrounding the left hand was raised to 41 C while that of the water surrounding the right hand was lowered to 25 C Blood flow increased in the cooled hand and decreased in the warmed one Fifteen minutes later the temperature was changed from 41 to 25 on the left side and from 25 to 41 on the right Blood flow in the cooled hand rose from 9 to 33 ml /100 ml hand/min while in the warmed one it fell from 17 to 10

The inverse relation between local temperature and hand blood flow was confirmed in further experiments done on the

forty fifth forty seventh sixtieth and one hundred and twenty first days The effect was seen though not so cons picuously when the body was not warmed

Temperature responses were normal in the girl s feet They were also normal in another case of hyperhidrosis before sympathectomy and in two other sympathectomized subjects In another two sympathectomized subjects small vasodilator responses to cold were observed

The conditions of the appearance of the remarkable phe

FIG 1 Results showing an unusual relation between tem perature and blood flow in the hand In this subject cooling the hand increased its blood flow and *vice versa*

Hand blood flow measured by venous occlusion plethysmography The temperature of the water in the plethysmographs was initially 3?–33C Changes in water temperature indicated under the upper margin of the figure Subject s body warmed during the time indicated by the shaded rectangle

nomenon seen in Fig 1 are at present unknown as also is its explanation

In the second part of this paper we wish to bring forward for discussion the notion that in muscular segments of human limbs (and we believe in the muscle itself) there are two functionally independent circulations one subserving meta bolism and controlled by local conditions and another concerned perhaps with circulatory homeostasis controlled by sympathetic nerves and by certain hormones

The evidence is of two kinds First the apparently discordant results of plethysmographic and ^{24}Na clearance methods of estimating muscle blood flow and secondly the lack of interaction between hyperæmia induced by exercise and that produced otherwise

The evidence of the first kind is summarized in *Table I* which is based on the findings of various workers

Table I

	Plethysmographic Flow	*^{24}Na Clearance*
Exercise	+	+
Circulatory Arrest	+	+
Body Heating	+	—
Adrenaline	+	—

It will be seen that the methods agree when hyperæmia is provoked by local means but differ when the cause is remote If we accept the findings at their face value we must conclude that the methods are not estimating the same variable This is not surprising *the plethysmograph measures the flow* irrespective of the channels used while the ^{24}Na clearance measures the rate of turnover of the interstitial fluid This will depend on the metabolic flow i e the flow through vessels having sufficient large diffusing area to make the blood/interstitial concentration gradient small For example in Fig 2 the total flow might be the same in A and B but the ^{24}Na clearance would surely be higher in B Variations in flow pattern of the type shown must be considered possible in the light of the work of Zweifach (1949) even in the absence of anatomically differentiated shunts

We now turn to the second kind of evidence The hyperæmia following exercise is related to the severity of the exercise and is usually regarded as repayment of a metabolic debt Hyperæmia induced in anticipation of exercise might be expected to reduce the debt and the consequent post exercise excess flow *In fact hyperæmia induced by body*

heating or by adrenaline leaves the post exercise excess unchanged (Barcroft Dornhorst McClatchey and Tanner 1952 Dornhorst and Whelan 1953) Dornhorst and Whelan also observed that the increase in flow during a sustained contraction of forearm muscle was uninfluenced by simultaneous hyperæmia produced by adrenaline

In all these examples the two types of hyperæmia appear

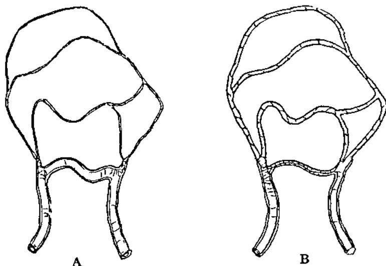


FIG 2 Hypothetical schema of the vessels in skeletal muscle showing metabolic and anastomotic vessels Total flow as measured by the plethysmograph is the same in a and b ^{24}Na clearance is greater in b

to summate without interaction The simplest explanation is surely that they are occurring in different sets of vessels

It is of interest that Quensel and Kramer (1939) found that in their dog muscle preparation coincident dilatation with acetylcholine did in fact lessen the post exercise excess It would be interesting to try this in man If it worked one would predict that it should also increase the ^{24}Na clearance

There are of course difficulties not the least being the absence of any anatomical evidence Moreover if one endows

the shunts with Burtonian critical closing pressures the situation becomes rather complicated However the facts are such that an attempt to preserve the functional homogeneity of muscle vessels will involve some even more complicated hypothesis

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DISCUSSION

EDHOLM *The two papers are now open for discussion the main themes are of great interest* It is a remarkable finding that in certain circumstances there may be vasodilatation in cool water and vasoconstriction in warm water Some of the problems regarding the extent and direction of a local vascular response may be clarified by the relationship between body temperature heat flow and blood flow described by Dr Kerslake Then there is the suggestion that there may be two types of circulation through muscle one responsible for local metabolic needs and the other responding to more general stimuli

BURCH I wonder if many of the measurements presented may not be due to errors produced by overfilling of the veins with leakage past the occluding cuff When the flow is rapid through the finger tip erroneous impressions of the rate of blood flow can be obtained due to excessive filling of the venous reservoir This is particularly prone to occur following heating of the subject

EDHOLM *Were these sympathectomized subjects?*

BURCH We did not study sympathectomized people

BARCROFT I very much hope that Dr Burch will come and visit us sometime* so that we shall have the pleasure of showing him some of our tracings It certainly was an omission on my part not to have brought any of the actual records with me but perhaps he will accept my word for it that in doing the blood flow in the hand and forearm the situation is quite remarkably different from the finger tip and that for five or even ten seconds one can continue collecting the blood from one heart beat after the other and draw a completely straight line through the record

*A visit to Dr Barcroft s laboratory following this meeting with a study of the original tracings indicated that his findings appeared to be genuine observations from the qualitative point of view The work needs further study —C F B

There is a striking difference between these more proximal parts and the finger tip

DAWES That is because the venous volume is greater?

BARCROFT Yes

BURTON I agree entirely with Dr Burch that Professor Barcroft s results are utterly subversive at least to stable physiology and I think at all costs we must prevent him from ever telling medical students about this sort of thing The progress of science however depends upon people putting forward subversive ideas and subversive results

I wonder whether there is not something in what Dr Burch said that would help us to look for an explanation of these fantastic results My feeling is that in the absence of any other clue he might study what is happening in the veins I do not agree that in measuring forearm flows this artifact due to the veins being fuller and the curves turning over quicker would make these measurements invalid but I do think that I would like to know what is happening in the veins when you warm these sympathectomized arms Are they in effect getting fuller? You might get evidence of this by leaving the occlusion on long enough for the curve to reach the top and see how much the volume increase was because the curious effect that Dr Gaskell has shown with posture in the digit is present in a sympathectomized limb I do not know how maybe it is a local reflex I wonder whether perhaps an explanation could be that when you warm the limb the veins for some reason are fuller and thus causes some reaction which brings out a vasoconstriction?

GREENFIELD Perhaps a calorimetric observation would help to dispose of Dr Burch s doubts

SHEPHERD In relation to Prof Barcroft s communication Dr Patterson and I have made similar observations using vasodilator drugs instead of release of sympathetic vasomotor tone to increase the forearm blood flow The drugs used were magnesium adenosine triphosphate histamine and acetylcholine Infusion of any of these substances into the brachial artery in a dose sufficient to more than double the resting flow and maintaining this infusion during and after rhythmic standard exercise of the forearm muscles has no effect on the debt repaid or its rate of repayment Each of these three substances when given intra arterially in suitable doses powerfully dilates the forearm vessels It is thus unlikely that their action is confined to sympathetically innervated vessels and we assume that part at least of the increased flow is through vessels concerned in metabolic exchanges In spite of this the blood debt is repaid and its rate of repayment is unaltered

Whatever the explanation of our results it is unlikely that they can be explained on the basis of two pathways through muscle

WHITNEY From an anatomical point of view I thought that Zweifach described arterio venous connections in the vascular bed in skeletal muscle?

DORNHORST Yes Zweifach is a little reticent in saying what structures are present because he does use the term preferential channel essentially in a functional sense It might be just a temporary behaviour

of ordinary capillaries and it is difficult to find out whether he has seen more or less permanent specialized channels

Whitney He certainly does say that there are capillaries which remain open irrespective of the state of vasodilatation or vasoconstriction of the capillaries as a whole Although he is not explicit on the point he does rather imply that these are arterio venous connections

Dornhorst That is what we hoped

Edholm I think everyone would like to find A V shunts in muscle vessels but those who have looked for shunts have failed to find them Is that correct Professor Barcroft?

Barcroft Zweifach has seen such communications in the tibialis *anterior and the soleus of the cat and in the rectus abdominis of the* mouse Unfortunately no photographs of his preparations are available

Dible There are certainly alternate arterial by paths in muscle which are quite easy to demonstrate There is no question of A V shunts at all I have demonstrated these by paths in the soleus and in the gastrocnemius muscle in the amputated limb in man I hope to be able to show you some pictures of them tomorrow The pictures when the vessels come into function are exactly the pictures which Dr Dornhorst showed us of two alternate routes one going through the capillaries of the muscle and presumably involved in the metabolic exchanges of the muscle and the other a simple arterial short circuit

Asmussen Don t some of the vessels running through the muscles also supply the skin?

Dornhorst It is a long story and rather an ancient battle but I think most people are willing to accept the skin as not being responsible For instance with adrenaline hyperæmia the skin is quite notably blanched and where you can measure it the skin flow is down We did refer to muscular segments of limbs because it is conceivable that some other structure is involved but it is not easy to picture what that would be other than the muscle

Grant As regards these arterio venous anastomoses I think there is a whole series of vessels from wide capillaries up to the specialized structures which have been described in the human finger etc I have seen them for example in the human nose where there is a change from artery to vein without any intervening structure In human muscle I have not found any of the specialized structures with the so-called epithelial cells in the wall You might make observations on animals you might be able to see the vessels in some thin muscle sheet and apply these stimuli and see whether there is a different circulation during exercise or as a result of warming the body You might thus see if there is one channel for the one stimulus and another channel for the other stimulus Histologically you could not differentiate

Greenfield I was fascinated by Dr Kerslake s paper and by his very interesting idea which seems to be that as soon as heat goes through the skin *in either direction* you put on more physiological clothing in effect you raise the surface insulation I am wondering how Dr Kerslake would integrate this idea with the frequent need of the body to get rid of heat because it is making too much and is getting too hot

KERSLAKE The curves I showed can be replotted on the assumption that the rate of heat loss is proportional to the product of the blood flow and the difference between deep temperature and skin temperature In this way one obtains a relationship between deep temperature and skin heat flow at any given skin temperature Now since skin temperature has been shown experimentally to be determined almost entirely by the environment then in a given environment the skin heat flow will be determined by the deep body temperature In the steady state there will be an almost linear relation between deep temperature and metabolic rate At high skin temperatures this relationship ceases to be linear In the same way an environmental stress in the form of a decrease of thermal acceptance would be expected to produce a slight change of deep temperature and the attainment of a new equilibrium at a new skin temperature These predictions are in accord qualitatively with experimental observations and indicate that the system postulated is consistent with some of the known facts The assumed relation between heat loss and blood flow is almost certainly inexact and I should not wish to attach too much weight to this extension of our data

EDHOLM Do you think that your findings throw any light on the problem of what is the maximal blood flow?

KERSLAKE We never observed a maximal blood flow The highest we obtained was at zero heat flow and about 39 ° C mouth temperature Here the flow was of the order of 100 ml /100 ml hand/min and oddly enough was quite measurable Hand blood flows at lower mouth temperatures or higher heat flows were less than this and there was no evidence that the limit of blood flow had been reached

DORNHORST These experiments sound as though they are uncomfortable were they?

KERSLAKE The question of thermal comfort was quite interesting as comfort was related chiefly to bath temperature and seemed to bear no relation to the physiological strain as evidenced by the hand blood flow Prolonged exposure to a bath at 42 C which at first was entirely acceptable did eventually lead to some restlessness and complaints of fullness in the head These were immediately relieved by lowering the water temperature

HERTZMAN I was very much surprised that you could get such a great dilatation In our observations in a hot room we found that palmar sweating starts up when the evidence of discomfort appears But I would have expected it to be followed by some evidence of vasoconstriction At lower temperatures palmar sweating is not excited by a rising environmental temperature although full dilatation apparently exists

KERSLAKE We tried to avoid apprehension on the part of the subject by allowing him to call a halt at any time he wished The water temperatures used were not high enough or low enough to cause any sort of pain and the only unpleasant symptoms were those rather vague ones I referred to just now which occurred after a long period of heating

HERTZMAN Our subjects complained and this change occurred when they noticed discomfort they began to get a little restless and so forth

They were not miserable just uncomfortable and yet they had no feeling of danger or anything else

KERSLAKE I think most people would agree that the effect of psychic factors on blood flow is smaller when the blood flow is high In our experiments the subjects were only uncomfortable when the hand blood flow was very high since at a high mouth temperature an increase of heat flow to the limit imposed by the subject s tolerance will only reduce flow by a small proportion

GRANT There is one point which has not been raised and which might help to explain the changes It is known now that the arterial wall contains substances like adrenaline and acetylcholine it also contains enzymes—the pseudo cholinesterase and mono amino oxidase It may be that under one set of conditions you may have a certain amount of enzymes present and by adaptation you get a changed amount of enzyme or of the acetylcholine or the adrenaline present I think these possible changes have to be borne in mind when one is discussing the changes in blood flow of the part as a result of adaptation to cold or heat

CARLSON I was very much intrigued by Dr Kerslake s presentation also but I am not clear whether in general the regulation is a combination of a peripheral stimulus superimposed on the central situation I think this would then be related to the rate of change in the periphery and the area or the amount of change going on would you agree? I am interested in what the receptors for this may be and I wonder if Professor Bazett s contribution just recently would be in line?

KERSLAKE First of all I think that the heat flow through the skin must bear an approximate relation at constant metabolic rate to the rate of change of deep temperature Physiological relationships which have been claimed with the latter are therefore consistent with the hypothesis of control by cutaneous endings sensitive to heat flow

The afferent nerve impulses postulated by Bazett are related to temperatures in different parts of the vascular network in the skin The temperature gradients there must depend on skin blood flow as well as on heat flow and the necessary relationships would be complex The biggest difficulty arises in the case where the circulation to the heated skin is arrested As Cooper will show this afternoon reflex blood flow responses do not appear to be altered by this procedure and this makes it improbable that the temperatures of the vascular layers of the skin are directly concerned Furthermore Bazett s investigations were based on thermal sensation and we have found that the afferent pathway can be destroyed without producing any obvious change in the thermal sensation from the affected area This observation divorces the nerve endings associated with reflex control of skin blood flow from those subserving thermal sensation and there seems to be no need to suppose that the two systems should be stimulated in the same way

CARLSON The demonstration by Hensel and Zotterman on cold endings is rather interesting here because with a change in temperature there is a rapid firing and then a new level

KERSLAKE We have also been interested in the warm ending they

have described in the cat s tongue which has a peak response at about 40 C falling off on both sides This is very difficult to distinguish from a heat flow ending if body temperature is in the region of 40 C and the ending is situated at a suitable depth in the skin

ASMUSSEN There is one observation of Skoglund on cold receptors I would like to mention he found that the number of active cold receptors increased with increase of skin temperature And another point also by Skoglund that may have some bearing on Barcroft s work, by stimulating a small area of the skin by cold he found an increase in the muscle temperature underlying the cooled skin area and his conclusion was that it was caused by a dilatation i e an axon reflex dilatation of the muscle vessels underlying the cooled skin area

BURTON I want to point out that Dr Kerslake s theories and ideas are also subversive to good sense and to general physiological theory First of all from the point of theory Dr Carlson was talking of Bazett s ideas about receptors that respond to gradients I cannot see how one could devise a receptor which responded to a gradient in the same manner whichever way that gradient went Nor can I see that such a response would be useful to the organism—after all a receptor will be required to respond the opposite way if the gradient is the other way Then again Dr Bazett s experiments showed that these reversed gradients gave the paradoxical sensation etc and Dr Kerslake has admitted that as to sensation his ideas are different Are we going to differentiate sensations of temperature from the reflexes aroused by temperature? If we are this becomes very difficult on general biological theory doesn t it? And I und rstand that Dr Cooper is going to be even more subversive

OBSERVATIONS ON THE NEUROHISTOLOGY OF CUTANEOUS BLOOD VESSELS

G WEDDELL and W PALLIE

Introduction

A description of the innervation of the cutaneous blood vessels presents the histologist with a difficult task The nerve fibres concerned when they emerge from the cutaneous plexus range from 8μ to less than one micron in diameter and their terminals are numerous and overlap and inter twine with one another in a complicated manner thus their arrangement and mode of termination can only be studied under the microscope at the highest magnification This demands that the methods by which specimens are prepared for microscopical examination must be impeccable and artifacts must be reduced to a minimum or else the description given may include details of magnified artifacts which would render it useless in the study of function

Many accounts of the innervation of blood vessels have been given for example that of Woollard (1926) of Stohr (1935 1951) of Nonidez (1936) and of Nelemans (1948) When the observations of different authors are compared however they are found to vary so greatly that it must be concluded that the histological techniques at present available are not adequate to allow of a detailed functional interpretation of any particular morphological description Attempts have therefore been made to develop new neurohistological tech niques for the display of tissue neural elements which are free from such a limitation In this communication preliminary observations on the mode of innervation of cutaneous arteri oles and capillaries in the rabbit rhesus monkey and in man based upon the use of these new techniques will be given

Material

1 Skin from the dorsum of the ear of the rabbit

2 Mucous membrane from the glans penis of the rhesus monkey

3 Skin from the human forearm

Methods

1 *Histological* For a full account of the methods and the rationale of the procedure see Weddell and Zander (1950 1951) and Weddell and Pallie (1953) Briefly the living skin before removal is treated with hyaluronidase by local infiltration Some twenty minutes later the skin is either removed fixed and frozen sections of it impregnated with silver according to the method of Bielchowsky Gros or injected with methylene blue and subsequently prepared for microscopical examination as a whole preparation Although in this communication we are confining our observations to the nerve supply of arterioles and capillaries it is interesting to note that the nerve supply to the arteries is best displayed if collagenase is infiltrated into the skin after it has been treated with hyaluronidase and before it is stained with methylene blue or impregnated with silver

2 *Experimental* (a) Small nerve bundles at the base of a rabbit ear were excised after the area they subserved had been mapped by electro physiological means Forty eight hours later both ears were stained with methylene blue in order to discover the number and distribution of the degenerating nerve fibres

(b) A superior cervical ganglion was removed in each of three rabbits Forty eight hours later in the case of two animals and seven days later in the case of the third both ears were stained with methylene blue and examined in order to discover the number and distribution of the degenerating nerve fibres

(c) An entire cervical sympathetic chain and stellate ganglion was removed in each of four rabbits Seven days later in each case both ears were stained with methylene blue

and examined in order to discover the number and distribution of the degenerating nerve fibres

Observations

Normal Skin The aim of the technique is to display the neural elements specifically so that their appearance is comparable with the undamaged neural elements in fresh sections from the living untreated cornea seen under phase contrast conditions In the case of the skin this is achieved and attention is paid to detail throughout the preparation of specimens for microscopical examination

The treatment with hyaluronidase enables the skin to be fixed without distortion of the nerve fibres and the production of artifacts It also enables the silver salts or methylene blue to reach the nerve fibres in even concentration throughout the specimen so that the depth of impregnation or staining is uniform and can be controlled at will

In the specimens of skin chosen, the only vessels whose innervation has so far been studied in any detail are the arterioles and capillaries Casual observation however shows that the pattern formed by the arteries and veins is essentially similar to that formed by the cutaneous nerve plexus for they run side by side throughout most of their course

Arterioles The arterioles are supplied by stem axons surrounded by Schwann cell sheaths which run close to and parallel to the vessel The stem fibres are unmyelinated and of small but uniform diameter (1 3μ) They reach the vessel in bundles of four to six fibres which emerge from the cutaneous plexus after a complicated course during which they branch freely It has not yet been possible to enumerate the branches nor to trace the stem fibres through the cutaneous plexus to their origin from the peripheral nerve trunk supplying the zone of the skin in question Such an analysis is very difficult and time consuming for although the actual distance from the entrance of a parent fibre into the cutaneous plexus to the emergence of a particular branch to reach an arteriole



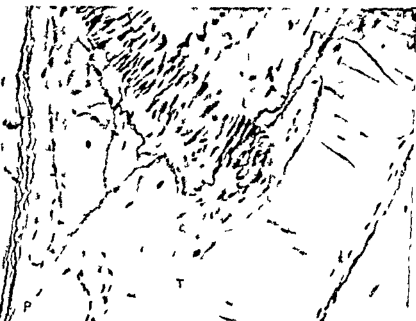


Fig. 1. The figure is from experimental material and many vascular nerve fibres have degenerated and can no longer be seen. It has been selected to illustrate the one observation which we should like to stress above all others: it shows stem nerve fibres giving rise to fine naked freely ending axoplasmic filaments. The specimen is a rabbit ear slightly overstained with methylene blue following infiltration with hyaluronidase seven days after excision of the superior cervical ganglion of the sympathetic chain on the same side.

Some of the smooth muscle cells encircling the arterioles are stained, particularly those around the smaller vessels. The Schwann cells surrounding the smaller isolated nerves are also stained.

Two stem nerve fibres (I) arising from a bundle to the left of the picture pass towards the vessels and they give rise to terminals (T) at intervals. Terminals from neighbouring stem nerve fibres can also be seen. × 640

may be only 0 5 cm analysis has to take place at a magnification of at least five hundred

At intervals along the course of the vessel offshoots from stem nerve fibres give rise to a large number of extremely fine naked axoplasmic filaments (less than 1μ in diameter) which terminate freely in slight enlargements the stem nerve fibres themselves end in a manner exactly similar to this The terminals lie on the surface of the smooth muscle fibres at right angles to their long axis They are not orientated nor do they terminate in any specific relation to the muscle cells (Fig 1) Axoplasmic filaments from neighbouring stem fibres overlap and intertwine so closely with one another that at low magnifications the terminals have the appearance of a continuous nerve net This appearance is also seen at high magnifications if the specimen has been damaged in the course of preparation

Capillaries No nerves were seen to end in any constant relationship to capillaries Nevertheless capillaries are surrounded by numerous nerve fibres which terminate close to their surface as well as in their immediate neighbourhood Both myelinated and non myelinated stem nerve fibres surrounded by Schwann cell sheaths emerge from the cutaneous nerve plexus In skin from the areas chosen the stem fibres can be seen to branch from other fibres in the cutaneous nerve plexus

Some stem fibres terminate in the form of an arborization of fine naked axoplasmic filaments situated just beneath the basal layer of the epidermis Each filament gives rise at intervals to terminals some of which pass vertically to end freely in between cells of the stratum germinativum and others end in very close relationship to the capillaries The area covered by the terminals from a single stem fibre is difficult to determine in normal skin for the axoplasmic filaments from the neighbouring stem nerve fibres intertwine and overlap so extensively with one another this area is however extensive and in the case of the human forearm reaches several square centimetres

Other stem nerve fibres give rise to similar naked freely ending axoplasmic terminals situated throughout the dermis and similarly intertwining and overlapping with their neighbours The terminals cannot be said to end in a constant relationship to any particular structural component of the dermis nor to any particular part of such a component although a greater number of filaments and terminals can be seen where capillaries are most abundant

The overlapping and intertwining of all the fine naked axoplasmic terminals so far described is most intimate towards their termination and if they are damaged there is as a result an appearance of terminal nerve fusion and net formation The distance separating one terminal from another may be as small as one micron

In the glans penis numerous encapsulated nerve endings are demonstrable The stem nerve fibres ultimately give rise to a series of naked freely ending axoplasmic filaments which end among the cells of the capsular wall In some superficially situated terminals branches from the stem nerve fibre have been seen to pass through the wall of the capsule to give rise to a series of naked terminals which intertwine with and are distinguishable from those found in the epidermis and those ending in the dermis They thus come into intimate relationship with the capillaries

Denervated Skin So far our observations on denervated skin have been limited to three groups of experiments

(a) A small nerve bundle at the base of the rabbit ear was excised on each of three occasions after the approximate area of skin which it subserved had been determined by electrophysiological means Forty eight hours later the ear was treated with hyaluronidase and stained with methylene blue and the area originally outlined and the skin surrounding it examined

Degenerating nerve fibres were seen throughout the area mapped and beyond it It was further noted that within the zone involved there were no areas devoid of nerve fibres or free from degenerating fibres In particular degenerating

nerve fibres were seen lying among normal fibres ending in relation to arterioles Similar observations were made in the case of the nerve fibres ending in relation to the epidermis and in the dermis

(b) The superior cervical ganglion of the sympathetic chain on one side was excised in each of three rabbits Examination of both ears forty eight hours later in the case of two animals showed degenerating nerve fibres ending in relation to arterioles side by side with normal terminals scattered evenly throughout the ear on the operated side only In the remaining animal which was examined one week after operation a reduced number of nerve fibres and terminals were seen ending in relation to the arterioles (Fig 1) The terminals ending in relation to capillaries seemed to be unaffected

(c) The cervical sympathetic chain including the stellate ganglion on one side was removed from each of four rabbits Examination of both ears one week later showed that the number of nerve fibres and terminals ending in relation to the arteries was considerably reduced Comparatively few nerve fibres were seen ending in relation to arterioles The terminals ending in relation to capillaries again seemed to be unaffected

Discussion

Preliminary observations suggest that the new technique gives consistent results and that the mode of termination of nerve fibres in relation to blood vessels is essentially comparable with the way the nerves end in fresh sections from the living untreated cornea when seen under phase contrast conditions For this reason it is perhaps permissible to discuss the functional significance of our observations In the first place it is clear that the vascular nerves which we have studied may be considered to consist of two parts stem nerve fibres and terminals

Stem nerve fibres reach the arterioles directly from the cutaneous plexus The stem nerve fibres which give rise to terminals which end in relation to the capillaries also arise from the cutaneous nerve plexus but proceed to the epidermis

dermis and encapsulated nerve endings rather than to the capillaries directly The stem nerve fibres whatever their destination are all surrounded by Schwann cell sheaths

The terminals all consist of a series of fine naked axoplasmic filaments which intertwine and overlap extensively with those from neighbouring fibres They form a network around the arterioles and end in close relation to the capillaries

The morphological contrast between the stem fibres and the fine axoplasmic terminals suggests that there may be some difference in their physiological behaviour, there is in fact indirect physiological evidence that there is Alvarez Buylla and Ramirez de Arellano (1953) have shown that mechanical stimuli of low amplitude evoke no response in the parent nerve fibre of a Pacinian corpuscle When the amplitude is increased a local response can be recorded up to 4 mm from the corpuscle The amplitude of the response increases *pari passu* with the amplitude of the stimulus until at threshold a propagated disturbance emerges from the late part of the local potential Now the stem nerve supplying a Pacinian corpuscle gives rise to a series of fine naked freely ending axoplasmic terminals which end within the wall of the corpuscle in the same way as stem nerve fibres give rise to terminals ending in relation to arterioles and capillaries (Weddell and Pallie 1953) It is thus tempting to conclude that a similar mechanism obtains in each case

If we assume that this is true then a morphological basis for the so called nocifensor system of nerve fibres (Lewis 1942) no longer presents an insoluble problem It will be remembered that his observations suggested that there was a dorsal root efferent system of nerve fibres which formed a continuous network just beneath the epidermis and which were associated among other things with the spread of flare and with hyperalgesia Lewis believed this system to be separate from the sensory system of pain nerves Wollard *Weddell and Harpman (1940) on the other hand, argued on* the basis of their histological observations that they were one and the same system

If the hypothesis we have propounded is acceptable this divergence of view disappears The terminals ending in relation to the capillaries are so disposed that local responses (resulting from a relatively light stimulus and involving short segments of neighbouring terminals) might easily spread far enough in the system of terminals and would in this case constitute a physiologically independent system this is in complete accord with Lewis s conception of a nocifensor system behaving independently of the sensory system of pain nerves

The independence that Lewis demanded seemed to him to require a separate system of nerve fibres but it is suggested that our observations and the hypothesis we have erected makes this unnecessary for we have suggested that the two parts of the single system may function independently of one another

The association of hyperalgesia with the nocifensor system strengthens our hypothesis for the presence of flare would suggest that only the slightest additional stimulus would be necessary to build up the strength of the local response sufficiently for it to initiate a propagated action potential in the parent pain nerve fibre It is of course assumed that the local response is connected with chemical changes concerned in the release of substances which influence the state of the capillaries

If our interpretations concerning the nocifensor system are correct the functional significance of the terminals ending in relation to the arterioles and elsewhere may be greater than is usually supposed and would strengthen the arguments of those who still believe that sensory nerves have trophic functions in the skin

Our experimental observations are inconclusive as to the source of the fibres reaching arterioles and capillaries In so far as they go they suggest that the nerve fibres supplying arterioles come from both autonomic and somatic sources However it is impossible to be certain that a few autonomic ganglion cells do not lie somewhere between the

superior cervical ganglion and the arterioles Thus the nerve fibres remaining after complete removal of the cervical sympathetic chain and stellate ganglion may not, in fact originate from the dorsal roots Ganglion cells have been reported (Nelemans 1948) although we have never seen any in the rabbit ear, despite the examination of hundreds of well stained specimens

With regard to the capillaries the majority of nerves terminating in relation to them would appear to arise from somatic sources Unfortunately we have not yet had time to make any quantitative investigations as to the number of stem fibres derived from any particular source

The terminals derived from stem fibres subserving encapsulated nerve endings which terminate in close relation to capillaries are of interest for they are probably the morphological basis previously described as underlying the axon reflex The difficulty of tracing the branching nerve fibres accurately throughout their ramifications in the cutaneous nerve plexus has prevented us from demonstrating the morphological basis of axon reflexes which have been demonstrated physiologically

Finally our experimental evidence together with the examination of normal specimens argues strongly against the existence of a terminal syncitial nerve net However as has been indicated from the physiological point of view the formations described may well behave as an independent peripheral entity This compromise is comforting to some histologists for the neuron theory which has been frequently attacked in recent years seems to be one of the few neuro anatomical concepts which have survived

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DISCUSSION

HERTZMAN I should like to get Dr Weddell s reactions to some observations which Dr Randall made in stimulating sudomotor fibres in the human being in relation to the question of a nerve net versus a sudomotor unit He has seen individual glands responding here and there as though they were innervated by one sudomotor fibre which had dichotomized It would have been difficult to explain that by the concept of a nerve net

WEDDELL Quite right We have actually seen that in human skin—a fibre dichotomizing and each branch going to a different gland

DORNHORST Am I right in interpreting Dr Weddell s findings as showing that after sympathetic denervation the majority of these fine fibres disappear?

WEDDELL That is so in the case of arterioles but nerve fibres ending in relation to capillaries seem to be hardly affected

DORNHORST After sensory nerve section or root section is there a different pattern?

WEDDELL Yes The nerve endings in the epidermis disappear If they happen to be encapsulated endings you just see the remnants of the capsules Some degenerating fibres are however seen in relation to arteries and I believe arterioles as well

CARLSON I am not sure I am clear about some of your suggestions I understand the local response becomes a sink so that presently your fibre will fire Is this local response then propagated on other fine fibres which perhaps have a different function?

WEDDELL I was afraid somebody would ask that I just do not know

DORNHORST If these naked fibres run within less than $\frac{1}{2}\mu$ of each other I should have thought that direct transmission was possible

WEDDELL Yes I think you are right

GREENFIELD Can you get rid of all the fibres if you cut the sympathetic and the posterior nerve roots or in any other way?

WEDDELL I wish I could give you an unequivocal answer Although the rabbit ear is the ideal place to see nerve fibres it is extremely difficult to cut the cervical roots supplying the ear with survival of the rabbit and we have not yet succeeded in doing this

GRANT Can t you get rid of all the fibres if you cut all the sensory nerves as well as the sympathetic including the Alderman s nerve (the auricular branch of the vagus)? I did it some years ago and I could not see any fibres afterwards

WEDDELL. I am sure you are correct and I shall try to repeat your experiments I imagine it is a difficult procedure Can you be sure that all the nerves are cut?

GRANT If you cut one nerve do the fibres of the other nerves sprout? I suppose they grow some distance

WEDDELL In the cornea they will grow right across it

GRANT I remember noticing in the rabbit s ear that if you cut both the great and posterior auricular nerves but leave the auricular branch of the vagus and then test the sensory responses of the ear this gradually spreads up towards the distal part of the ear you suspect regeneration but find there is still a gap between the cut ends of the auricular nerves I presume this is due to growth of fibres from the vagus?

WEDDELL It is indeed The progress of the spread can be assessed by pinpricks

VON EULER There is one observation which I think might be brought up in this connection and that is the peculiar occurrence of fairly large amounts of histamine in the post ganglionic sympathetic fibres So far no one has been able to give any satisfactory physiological explanation but it is a fact that in the pre ganglionic fibres for example in the cervical sympathetic the histamine content is relatively low but as soon as the superior cervical ganglion has been passed the histamine content is very high in all the post ganglionic fibres In the cow for instance the pre ganglionic fibres contain something like 20 micro grams/gram and the post ganglionic anything up to 100 micrograms/gram This is perhaps exaggerated in the cow but I believe it is the same relatively in other animals After seeing your photographs of the close connection between the two filaments the possibility of having a sort of chemical connection between them occurred to me—it might possibly give a clue to this peculiar occurrence of histamine

SOME ASPECTS OF THE REFLEX CONTROL OF THE CUTANEOUS CIRCULATION

K E COOPER and D McK KERSLAKE

The occurrence of vasodilatation in the hand when the legs are heated in warm water was studied by Lewis and Pickering in 1931 Pickering has shown that the increase in hand blood flow which occurs with this type of heating is dependent on the return of warm blood from a heated area Duthie and Mackay (1940) found evidence of an increase in hand blood flow on immersing the legs in warm water when the circulation to the legs was occluded Their work however was open to criticism on matters of technique and though suggestive was not conclusive

Heat from a radiant heat cradle applied to the trunk and upper thighs was found to give rise to vasodilatation in the hand (Fig 1) (Kerslake and Cooper 1950) The time of onset of this vasodilatation lay between ten seconds and fifteen seconds Such a response is rapid in comparison with the delay of ten to fifteen minutes observed in the warm water experiments quoted The latency of response during the radiant heat experiments seemed too short to be accounted for by the return of warm blood from the heated area This latter possibility was rendered even less likely by the finding in all but one of the trunk heating experiments of a fall in mouth temperature and coincident fall in both rectal and œsophageal temperatures

Further experiments designed to test the hypothesis that the hand vasodilatation during radiant heating depended on stimulation of nerve endings in the heated skin were performed A subject s legs were exposed to the radiant heat as far up as the mid thigh During the heating the hand blood flow increased the latency of the response being comparable

with that occurring during chest heating and the extent of the response being less (about half) when the legs were heated This experiment was repeated with wide cuffs round the upper

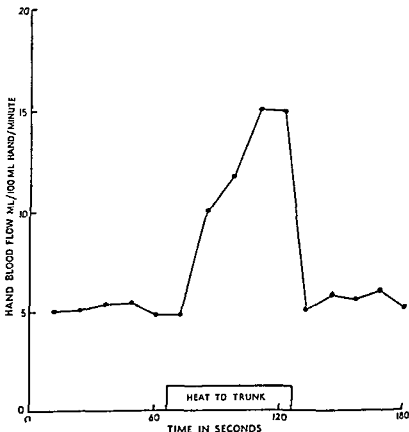


Fig 1 Changes in hand blood flow on applying radiant heat to the trunk are shown This curve is the mean of 10 identical experiments

thighs inflated to 250 mm Hg pressure and the response was unaltered The inflation of cuffs without heating the thighs produced no hand vasodilatation Similar results were ob

tained on several subjects and an example of this type of experiment is shown in Fig 2

From these experiments it is concluded that the thermal

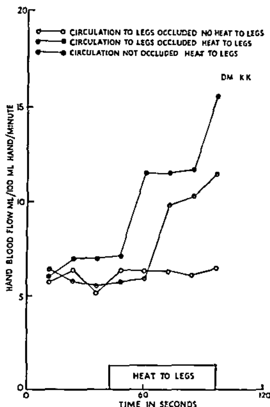


FIG 2 Leg blood flows during heating of the legs by means of a radiant heat cradle with and without arresting the leg circulation and also circulatory arrest without heat Each curve is the mean of three experiments

changes occurring in the skin area heated by means of a radiant heat cradle give rise to vasodilatation in the hand and that this vasodilatation depends for its initiation on

afferent nervous impulses arising in the heated area Such vasodilatation could be correctly termed reflex and it is felt that the term indirect" should be applied to the vaso dilatation produced by the return of warm blood which has been quoted previously

Further work showed that the forearm blood flow could also be raised by this reflex mechanism but when the skin of the forearm was rendered ischæmic by electrophoresis of adrenaline the response was abolished It appears therefore that the nervous reflex vasodilatation in the forearm occurs only in the skin (Cooper and Kerslake 1949)

An investigation was then begun into the anatomical pathways involved in reflex vasodilatation The first experi ments were performed on an elderly man who had undergone bilateral lumbar sympathectomy four months previously Heating the trunk was found to produce a vasodilatation of normal magnitude in the hand, but when the legs were heated there was no change in hand blood flow This result has been confirmed on two other patients and suggests that the afferent nerve fibres concerned in reflex vasodilatation are divided during the performance of lumbar sympathectomy On the other hand it was not known whether these patients had ever possessed a response to heating the legs and in view of the condition for which surgery had been advised it was necessary to establish on a further series of patients that the reflex was abolished by the operation

The vasodilator response in the hand to heating the legs was measured before and after bilateral sympathectomy in three patients A significant increase in hand blood flow was demonstrated before operation during a one minute period of heating One week after operation there was no evidence of such a response Confirmatory evidence was obtained by examining cases of unilateral lumbar sympathectomy A response was obtained when the normally innervated leg was heated but there was no change in hand blood flow when the sympathectomized leg was heated (Fig 3) In these experi ments radiant heat was applied for periods of two minutes

The time was kept short in order to avoid the type of vaso dilatation which results from the return of warm blood from the heated area and which has been shown to occur inde pendently of the innervation of the skin area heated (Uprus Gaylor Williams and Carmichael 1935)

The response has been shown to be abolished within one week of sympathectomy when the blood flow to the legs may

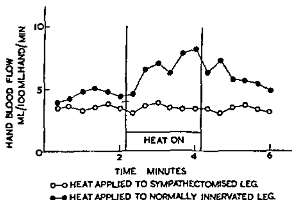


Fig 3 Changes in hand blood flow during leg heating

(a) when the normally innervated leg was heated and
(b) when the sympathectomized leg was heated

Each curve is the mean of nine experiments on three subjects

be high and is still absent after thirteen months when the resting skin blood flow has returned to a normal level (Lynn and Barcroft 1950) It is considered most probable that the afferent fibres are divided during the performance of the operation

The vasodilatation in the hand during heating of the legs could be due either to an increase or a decrease in the number of impulses passing up the afferent nerves In order to demon strate which of these phenomena occurs the lumbar sympa thetic chain has been directly stimulated This has been done

on patients during the operation of lumbar sympathectomy Nitrous oxide and scoline were used for anæsthesia One hand was placed in a plethysmograph and blood flow recorded in the usual way After exposure of the lumbar sympathetic chain with a minimum of trauma to it the chain was allowed to rest on silver silver chloride electrodes It was then stimu

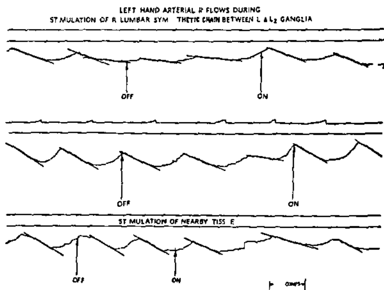


FIG 4 Hand arterial inflow curves during stimulation of the lumbar sympathetic chain The upper two traces show the reduced slopes of the inflow curves during stimulation The lower trace shows the inflows during stimulation of adjacent tissue All traces read from Right to Left

lated with square wave pulses of various durations and fre quencies (Fig 4) In two cases out of seven stimulation was found to produce a decrease in hand blood flow In the other cases no change was observed The constriction occurred within six seconds of the beginning of stimulation and passed off rather abruptly about ten seconds after stimulation was

stopped These times are comparable respectively with the latencies of the fall of blood flow at the end of heating and of the onset of vasodilatation at the beginning of heating (Kerslake and Cooper 1950) The abrupt increase of blood flow has also been demonstrated during heating The failure to demonstrate this effect in five cases is attributed to the difficulty of ensuring that the current passes through the nerve fibres and not through the adjacent connective tissue

The evidence suggests that there are afferent nerve fibres *running in the lumbar sympathetic chain which transmit* impulses from the skin of the legs and that the number of these impulses is reduced when the legs are heated The impulses appear to be associated with the reflex control of the cutaneous circulation

We are grateful to the editors of *J Physiol* for permission to quote data which has appeared in that journal and for permission to publish Fig 3

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DISCUSSION

HERTZMAN We have been able to confirm Drs Cooper and Kerslake in this work I just add the comment that when we had difficulties in inducing reflex vasodilatation in the foot by a heat bath we found that the difficulty arose from improper room temperature apparently one needs to have the thermosensory information at the right level in order to get this reflex triggered We discovered that a room temperature of about 28 was right for triggering the foot vasodilatation. The hand dilatation is triggered at a much lower temperature

DORNHORST I take it that in view of this morning s contribution Dr Cooper you interpret your stimulus as causing a decrease of heat flux?

COOPER Yes we would say that if the receptors discharge at a rate proportional to the thermal gradient through the skin then one would expect on heating the skin surface to have a decrease in the number of

impulses passing up the afferent fibres On stimulation of the afferent fibres therefore you would expect to produce only vasoconstrictor impulses from the reflex centre We have not yet done enough experiments in which the afferent fibres were stimulated over a wide enough range of frequencies and amplitudes to be able to say there are no such things as dilator afferent fibres

DORNHORST According to your contribution this morning an increased heat flux of the skin was accompanied by a decrease in hand flow Therefore you must assume that turning on your cradle has slowed an outward flux and you might expect to get a reversed effect if you started at a high ambient temperature with a non steady state and then increased the flux

KERSLAKE We have obtained constriction by intense radiant heating in the way you suggest but this is soon overcome by the vasodilatation caused by a rise in deep temperature due to the return of warm blood from the heated area

SHEPHERD I think this might explain why patients with intermittent claudication are occasionally helped by lumbar sympathectomy If you determine the maximum blood flow through the calf before and after lumbar sympathectomy there is seldom any increase after operation but many of the patients have some relief from the pain

FITZGERALD There is a rather crude clinical observation pointing I think to the presence of afferent peripheral sympathetic pathways Some years ago in sympathectomized patients I noticed that they did not appear to feel so much pain when their hand was resting in cold water as did normal individuals It was then found that if they grasped a cake of ice they could hold it for a long time An ordinary individual who does that gets a causalgic type of pain These people did not have pain although they could appreciate the fact that the ice was cold—there was no interference with their ordinary temperature sensation Furthermore we noticed that if we did a cold pressor test on people prior and subsequent to a lumbar sympathectomy the latter had less response to the cold pressor test we got a blood pressure which would appear to fit in exactly with the demonstration which you have presented I should have thought that this was a commonly known phenomenon

WEDDELL From the purely embryological point of view it is rather strange that the autonomic nervous system should be considered entirely separately from the nervous system as a whole From the point of view of convenience I can well understand why it is described separately but this seems to be a very good demonstration that it behaves as part of the nervous system as a whole and not in an entirely different manner

BURTON Dr Cooper has shown most convincingly that after sympathectomy you can get no disturbance of thermal sensation yet complete absence of this reflex pain Does the converse hold? If you take a patient with a profound disturbance of thermal sensation who has an intact sympathetic system is there any difference in his reflex dilatations?

COOPER We have made one or two observations on patients with *cauda equina* lesions They were patients with long standing lesions and atrophic skins We have not had any convincing demonstration of the presence of a reflex there What we need are some recent *cauda equina* lesions in which the skin is in a good state Then I think we shall be able to give you your answer

EDHOLM What about syringomyelia?

COOPER We have examined one case of syringomyelia in which no difference in the extent of the hand vasodilatation was produced by heating either limb one limb was anæsthetic and one limb appeared to have a normal sensation But I think we went a bit too far—we applied statistics to the dilatations which occurred and neither were significant

EDHOLM I wonder if Professor Greenfield can confirm Mr Fitz gerald s findings of differences in sensation between normal and sym pathectomized hands on immersion in ice water?

GREENFIELD We have observed only a few cases and we have not looked at them especially from the point of view of pain but we have not noticed any difference

HERTZMAN I can recall a particular case which provided really de cisive evidence on some of these supply questions Lumbar ganglionec tomy had denervated the foot as far as vasomotor and sudomotor activity was concerned in this patient Neither vasomotor nor sudo motor activity could be elicited in that foot yet causalgic pains con tinued unaffected The surgeon went in again and found a ganglion at L1 on its removal the causalgic pains disappeared and osteoporosis cleared up It was concluded that afferent visceral fibres entered the ganglion at L1 they were interrupted by removing the ganglion

WEDDELL Pain is a very difficult problem A relevant observation which cannot be discounted is that if the pattern of afferent stimuli associated with pain changes the quality of the response may become intensely unpleasant and *vice versa* Perhaps the conditions in the peri phery are altered following some sympathectomies so that there is merely a change in pattern of afferent pain impulses?

DALE Is there any hint as to where these sensory endings are placed? Are the sensory endings in the blood vessels or are they in the sub cutaneous tissue or where?

KERSLAKE We have no direct evidence about where these endings may be but we think that they may be sensitive to heat flow and that they may be superficial to the cutaneous vascular plexuses

DALE Therefore presumably in the epidermis and not in the dermis?

KERSLAKE Yes

BURTON Don t we need a new word instead of sensory if we have to describe these? After all sensory does imply a conscious sensation—you will have to invent a word such as autonomsensory

DALE No please don t I would agree with Dr Weddell with re gard to sensory fibres in the sympathetic system that the application to them of the word autonomic is quite inappropriate because it does not mean that Langley invented the word autonomic to mean a

nervous system the function of which was not dependent necessarily on any central connexion and which had ganglionic synapses

DORNHORST Is it not the case that the visceral afferent fibres which travel with the sympathetic actually relay in the posterior root ganglion like ordinary sensory fibres?

DALE Yes arise from ganglion cells but not relay

HERTZMAN The point should be made that the presence of these afferent fibres in the sympathetic trunk has been verified histologically by degeneration experiments

THE PROBLEM OF VASOMOTOR DENERVATION

A. B. HERTZMAN, W. C. RANDALL, J. W. COX, W. F. ALEXANDER and K. B. COLDWATER

It would be useful to open the discussion of the vasomotor denervation of the extremities with a review of the various anatomical, surgical and physiological data on the subject and of the ideas which have been offered in the interpretation of the data. The task is too large for our immediate purposes. I shall limit my statement to what may properly be called a promissory note respecting the vasomotor supply to the extremities. In the discussion of this subject I shall lean heavily on the laboratory's accumulation of a very detailed body of knowledge concerning the sudomotor innervation.

Our laboratory has been concerned for more than a decade with *vasomotor reactions in the peripheral circulation*. Both our published and unpublished experiences have focused our attention on several general questions: what is the vasomotor supply to the extremity? How does this innervation function? How may a satisfactory vasomotor denervation be effected?

I would like to suggest that the vasomotor reactions in the hands and feet are unique and not at all characteristic of other skin areas or of deeper tissues. I also submit that the problem of vasomotor denervation must be referred to particular vascular beds and that generalizations should not be applied to those vessels whose responses have not been observed directly. This point has been made repeatedly in the literature on vasomotor reactions. It still requires emphasis.

Cutaneous Vascular Responses in Relation to the Question of the Cutaneous Vasomotor Supply

Several lines of evidence demonstrate the unique behaviour of the arterioconstrictor supply to the palm and sole

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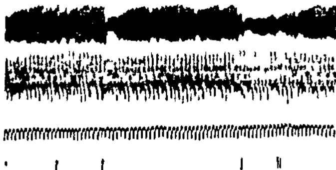


Fig 1 Cutaneous volume pulses Upper trace—finger pad middle trace—forehead (Courtesy— *Amer J Physiol* 136 J 1942?)



Fig 2 Volume pulses Upper trace—digital artery lower trace—finger pad (Courtesy— *Amer J Physiol* 134 ..J 1941)

(1) Cutaneous arterioconstrictor reflexes to such stimuli as noise and the local application of cold to another skin area are limited in our experience to palmar and plantar skin Thus such reflexes were not exhibited in recordings of the cutaneous volume pulses of the forehead (Hertzman and Roth 1942) or forearm skin (Fig 1) The method of conductance as applied by Hensel (1952) in his stream calorimeter likewise demonstrated only slight changes in the blood flow of the thigh skin under similar circumstances Further changes in skin temperature on the arm or leg follow rather than accompany or precede the changes in hand or foot blood flows I have also noted that such reflexes usually do not include arteries of the size of the digital artery (Hertzman 1941) An illustrative experiment is shown in Fig 2

(2) Possibly a more significant type of evidence is supplied when general changes in vasomotor tone are induced In unpublished experiments on the reactions to small hæmorrhages (in the human subject) I have had the opportunity to observe cutaneous vascular responses during a vasovagal syndrome Although most subjects exhibited reduction in the cutaneous blood flow following hæmorrhage, this one subject showed a marked dilatation in the finger when the reaction appeared *but* a reduction in blood flow in facial skin The decrease in flow there correlated with the fall in arterial blood pressure and appeared to be passive in character

The cutaneous vascular responses to changes in environmental temperature also illustrate the unique character of the vasomotor responses in the palm and sole The trends in data which we have obtained and reported elsewhere (Hertzman 1953) are illustrated in *Fig 3 The cutaneous blood* flows charted in this figure were estimated from recordings of the skin pulses Conductance data agreed in general with the pulse data One may note that as the environmental temperature rose palmar dilatation began first and plantar dilatation soon followed both increased rapidly while the dilatations in the skin of the head trunk arms and legs proceeded

Studies in Sympathetic Denervation

The experiments which are discussed below were instigated by recent anatomical studies which have demonstrated the variability in the gross structure of the sympathetic trunk and in its connections and also the existence of accessory pathways which do not pass through the sympathetic trunk (Alexander Kuntz Henderson and Ehrlich 1948) These data clearly indicate that the conventional resection of the ganglia at L and L_3 levels does not provide a complete pre ganglionic denervation of the lower extremity and also may not yield a satisfactory therapeutic result Our experience tends to confirm this statement

The Vasomotor Supply to the Dog s Hind Footpad

The procedure which was used in the identification of the vasomotor supply of the dog s footpad (Randall *et al* 1953) has also been applied successfully in the description of the sudomotor outflows in man (Randall *et al* 1952 Coldwater *et al* 1953) The method used the classical approach of direct electrical stimulation of the nerve fibres and observation of the effectors This approach has been used by others in the study of sympathetic pathways (Ray Hinsey and Geohegan 1943) The experimental technique described elsewhere (Randall *et al* 1953) is illustrated schematically in Fig 5 and explained in its accompanying legend Study of this schema will show that if the observational requirements are met the preganglionic inflows to the sympathetic trunk may be identified by the appearance of or by increments in the responses of the observed effectors as the stimulating electrodes are moved caudally along the trunk and that the postganglionic outflows from the trunk may be detected by stimulating the ganglion after the sympathetic trunk has been sectioned cranial and ca[illegible] ganglion This procedure was controlled in th[illegible]nts by subsequent serial section of the exc[illegible] trunk When the vasomotor responses in [illegible]ion of the

mental temperature The sudometer denervation in the observed area was known to be quite complete The argument is strengthened further by an observation of Bruch Hensel Poche Rotzler and Spang (1952) who showed that Priscol did not increase blood flow in calf skin although flow did increase in the toe Hensel's experiment cannot be explained by assuming that the effects are minimized by inherently low rates of flow in calf skin since an increase in flow of ten times above the resting control level is realizable with locally applied dilator drugs such as histamine or mecholyl (Hertzman and Randall 1948) Explanation must be referred therefore either to an extraordinary selectivity in the action of Priscol or an inherently high tone of the blood vessels of calf skin or the absence of an arterioconstrictor supply which might be responsible for their tone

Such experiences do not of course constitute proof that the arteriomotor supply to the skin is limited to the palm and sole Nevertheless the proven extreme vasomotor lability of the palm and sole correlates with the tendency of peripheral vascular lesions to locate there The corollary may be drawn *that the therapeutic objective of a vasomotor denervation of* an extremity may be brought about adequately in many cases by a sympathetic denervation of the palm or sole It is also quite possible that certain cases may require the interruption of visceral afferent fibres or denervation of collateral vessel or denervation *of the vessels of bone and muscle*

The question is How may the denervations indicated be obtained?

We have undertaken a systematic study of this problem The first phase of this laboratory s investigations dealt with the identification of the vasomotor supply to the hind footpad of the dog (Randall Alexander Cox and Hertzman 1953) A second phase is now concerned with sudomotor denervation in man (Randall Alexander Coldwater Hertzman and Cox 1952) (Coldwater Cox, Randall Alexander and Hertzman 1953) A third phase will examine the vasomotor innervation of the human extremity

require removal of the entire lumbar sympathetic trunk as far caudal as the L_6 or L_7 ganglion Earlier studies from this laboratory (Randall Alexander Hertzman Cox and Henderson 1950) demonstrated that a complete lumbar ganglionectomy may not provide total vasomotor denervation of the footpad due to the variable presence of accessory sympathetic pathways which do not pass through the lumbar sympathetic trunk

An extremely interesting facet to these studies was the extensiveness in the lumbar sympathetic trunk of the vasomotor supply to the dog s footpad Although we have no fibre counts available and know of no technique by which we might attempt the implied correlation the fact referred to is significant in relation to the extreme lability of the palmar and plantar vascular beds as pointed out earlier in this paper The dog s footpad is no exception An extraordinarily large number of small vessels a dense arterial mesh an extensive vasomotor supply and vasomotor lability characterize the palm sole and dog s footpad Such data caution against generalizations concerning the peripheral circulation from observations which have been made on these particular skin areas

The Sudomotor Outflows in Man

Although many closely related problems concerning sympathetic denervations remained for study in the dog the decision was made to transfer the study of sympathetic outflows to the human subject The stimulation procedure as *developed in the dog experiments and as illustrated in Fig 5* has been applied in an essentially similar manner to the patient undergoing sympathetic surgery The first phase of the human experiments has been concerned with the sudomotor outflows The great convenience of observing sweat gland activity has been a profitable guide in the design of *these experiments as well as the source of significant infor*mation The fact should be emphasized however that these studies on the sudomotor outflows are preliminary to the

sympathetic trunk indicated preganglionic inflows or post ganglionic outflows of vasomotor fibres the anatomist identified corresponding preganglionic and postganglionic rami The converse was not always true since the communicating rami and sympathetic roots were not concerned only

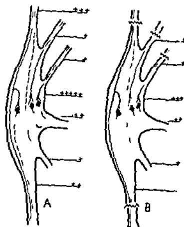


FIG 5 Schema illustrating the stimulation procedure used in the identification of the preganglionic inflows and the post ganglionic outflows from a sympathetic ganglion The fibre pathways represented are only those which are concerned with the effectors under observation No other fibre pathways are represented These pathways are represented as identical in the two figures which differ only in that the ganglion in figure B has been isolated by section of all connections excepting the sympathetic roots Preganglionic fibres are represented by solid lines postganglionic fibres by hatched lines intensity of response is indicated by the number of plus signs

Fig A—stimulation of preganglionic and postganglionic fibres

Fig B—identification of postganglionic outflows

with the innervation of the particular effectors under observation

The studies on the vasomotor innervation of the dog's footpad revealed such variable patterns of preganglionic inflows (and to less extent of postganglionic outflows) that a complete preganglionic denervation of the footpad would

require removal of the entire lumbar sympathetic trunk as far caudal as the L_6 or L_7 ganglion Earlier studies from this laboratory (Randall Alexander Hertzman Cox and Henderson 1950) demonstrated that a complete lumbar ganglionectomy may not provide total vasomotor denervation of the footpad due to the variable presence of accessory sympathetic pathways which do not pass through the lumbar sympathetic trunk

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investigation of the vasomotor innervation of the peripheral circulation It was hoped that the course of the sudomotor supply *to the particular* skin area *would* correlate *closely* with the corresponding vasomotor supply since the observation of vascular activity in a manner similar to that which is so conveniently available for the observation of sweating is much more complex difficult and awkward to effect at the operating table Nevertheless we must ask and eventually answer the question How dependable is the absence of sweating as an indication of corresponding deficits in the vasomotor supply to the affected area ?

The data now available on the sudomotor outflows to the lower extremity may be summarized in a simple statement the variability of the preganglionic and postganglionic connections of the lumbar sympathetic trunk is so marked that the standard surgical practice of removing the ganglionic masses located at the levels of the vertebral bodies of L_2 and L_3 *will not always interrupt completely the sudomotor* pathways through the lumbar sympathetic trunk As in the dog complete resection of the lumbar sympathetic trunk is necessary in order to increase the incidence of sudomotor denervation of the lower extremity We have been unable as yet to identify with certainty the presence of accessory pathways as postulated by others but the occurrence of considerable sweating in one case after a complete lumbar ganglionectomy *can scarcely be interpreted on any other* basis

Again as in the dog we have observed marked variability in the sudomotor outflows to the sole and dorsum of the foot This fact seems particularly pertinent to the surgeon s task and the interpretation of the therapeutic results Diffuseness in the outflows to the foot and the incidence of high and low levels of the outflows demonstrated that preganglionic denervation of the foot may require resection of the ganglion at L_1 or resection of the entire lumbar sympathetic trunk or possibly even interference at T_{12} We know of no way by which the situation obtaining in an individual patient may

be predicted The surgeon must choose between complete lumbar ganglionectomy or an analysis similar to that which we have employed of the fibre course obtaining in the individual patient

The significance of these observations with respect to the vasomotor supply to the foot remains to be determined Although our data are scarce the possibility of anatomical dissociation in vasomotor and sudomotor pathways is implied in several observations which will be described elsewhere

Post-operative Observations

The completeness of the sympathetic denervation of the lower extremity as effected by the analytical type of operation referred to above was examined in several ways *Thermo regulatory sweating* responses to environmental heat were measured by means of a dessicating capsule technique which has been analysed elsewhere (Peiss and Hertzman 1951) Sweating was also recorded by the sweat print technique which permits the counting of the number of active glands

The recruitment of thermoregulatory sweating in a normal subject with rising environmental temperature has been examined closely in our laboratory Descriptive details are available in several of our reports (Hertzman Randall and Peiss 1953) Fig 6 exhibits the regional sweating responses in several different skin areas of a normal subject exposed to progressively rising environmental temperature The implied opportunity of examining quantitatively the extent of sudo motor denervation is illustrated in Fig 7 in which has been charted the course of a similar experiment on a patient who had undergone a lumbar ganglionectomy previous to the experiment The extent and amount of denervation may be examined closely in this type of observation This technique is far superior to the essentially qualitative methods illustrated in measurements of electrical skin resistance or the colori metric methods of visualizing sweating responses It is impractical however in routine work because of the vast amount of labour required in a single experiment Essentially

the same information may be obtained by the simpler and less exacting technique of making sweat prints of the sweating areas Fig 8 exhibits the results of an experiment in which

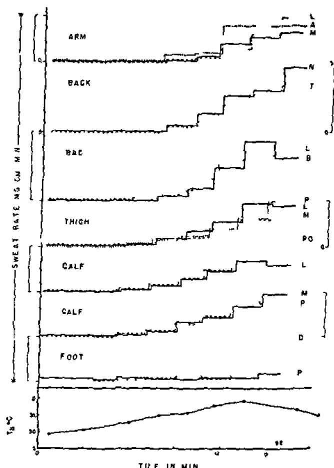


FIG 8 The effect of rising environmental temperature on the regional rates of sweating Reading down. Arm—lateral (L) medial (M) surfaces axilla (A) Back—neck (N) thoracic surface (T) lumbar surface (L) buttocks (B) Thigh—medial (M) lateral (L) and posterior (P) surfaces Calf—medial (M) lateral (L) posterior (P) and popliteal (PO) surfaces Foot—dorsal (D) and plantar (P) surfaces Sweat rates mg cm²/min

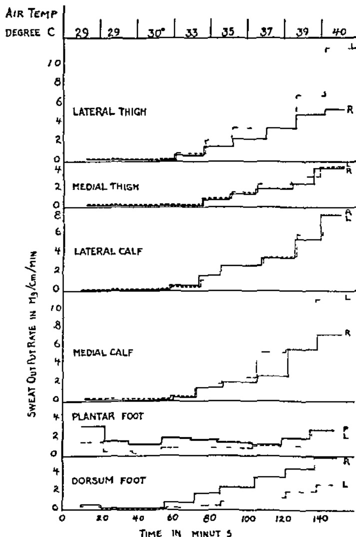


FIG 7 Thermoregulatory sweating on the lower extremity In clinical record of patient it was reported that a left lumbar ganglionectomy had been done previously Note absence of evidence of denervation Compare with figure 8

fibres The lesson of our experiments on the sudomotor out flows is clear the extremely variable and unpredictable patterns of these in various individuals necessitate either an exacting analysis of the pattern in an individual patient or complete lumbar ganglionectomy in order to secure sympathetic denervation Even then sudomotor denervation may be incomplete The application of this lesson to the problem of denervation of the vascular tree involves similarly quantitative studies of the vasomotor outflows not only to such a limited bed as in the toe but to the entire vascular tree of the extremity We have scarcely begun on this large and complex task

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[Discussion of this paper was postponed until after the paper by Dr Grant —Ed]

VASCULAR REACTIVITY FOLLOWING SYMPATHECTOMY

R T GRANT

RECENT observations suggest an explanation for the heightened reactivity that develops in the vessels of the rabbit s ear and the human finger deprived of their sympathetic nerves The explanation is that (1) the sympathetic nerves to these extremities contain fibres which normally exert a tonic dilator influence on the vessels through the release of acetylcholine and (2) the increased reactivity to constrictor stimuli following sympathectomy is due in large part to the interruption of these fibres and the gradual disappearance of acetylcholine from the vessels The evidence more complete *for the rabbit s ear than for the human finger is derived from* (1) the vasoactive properties of extracts of the central artery of the rabbit s ear and of human digital arteries and (2) the effect of atropine and eserine on the constrictor response to adrenaline in the ear and finger

Arterial Extracts Using a method of close arterial injection in the denervated rabbit s ear it is found that extracts *of normal central arteries and of normal human digital arteries* provoke a dilator followed by a constrictor response Since the dilator element of the extracts is inhibited by atropine and potentiated by eserine it is thought that acetylcholine is present in the extracts Extracts of rabbit ear arteries deprived of their sympathetic nerves at least a week beforehand still cause a dilator followed by a constrictor response of the test artery but since the dilator element is *neither inhibited by atropine nor potentiated by eserine* acetylcholine is thought to be absent For lack of material

the corresponding observations have not yet been made on human finger arteries deprived of their nerves

Evidence for Acetycholine Activity in the Living Animal

By close injection into the central artery of the rabbit ear *it is found (i) that to produce approximately equal constriction* requires a concentration of adrenaline 100 to 1 000 times more dilute in the sympathectomized than in the normal artery, (ii) that in the normal but not in the sympathectomized artery the constrictor effect of adrenaline is markedly potentiated by atropine and is inhibited by eserine These observations suggest that acetylcholine is present and active *in the normal but is absent from the denervated artery* Further observations as yet incomplete suggest that in the human finger the constrictor effect of adrenaline introduced by electrophoresis is potentiated by the preceding introduction of atropine and inhibited by eserine

It is known for both man and the rabbit that the heightened reactivity is not present at once after nerve section but de*velops over the course of days By testing the response to* adrenaline and the effect of atropine on that response at different times within the first week after nerve section in the rabbit it is found (i) there is no immediate change in the sensitivity of the central artery to adrenaline or in the potentiating effect of atropine on that response (2) as the response to adrenaline increases over the course of a few *days the effect of atropine decreases and (3) by the time* full adrenaline sensitivity is established atropine no longer potentiates the adrenaline constriction

The central artery of the rabbit s ear and human digital arteries exert both mono amine oxidase and pseudo cholin esterase activity In the rabbit artery sympathectomy reduces cholinesterase activity to about half normal Section *of both sensory and sympathectomy* nerves practically abolishes cholinesterase but leaves amine oxidase activity virtually unchanged

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DISCUSSION

LYNN We can corroborate Dr Hertzman s findings in the sympathectomized foot we have been interested in it for some time but being clinicians when we do a lumbar sympathectomy the anatomy in that region is sometimes a little vague and there are great normal anatomical variations anyway so we contrive to take out two ganglia We are not quite sure which two they are but we seldom go higher than the crus of the diaphragm and we seldom go down to the pelvic rim so we presume we take out L2 and L3 We have studied some of these patients as long as nine years after sympathectomy and all of the sympathectomies as far as vasomotor tone goes have so far been complete But in every instance we can demonstrate sudomotor activity by our electrical skin resistance methods We wonder from the clinical point of view how important these findings are?

HERTZMAN I think the last part of your comment is unanswerable at the present time We have a case in which the therapeutic results have been totally unsatisfactory from a complete lumbar ganglionectomy and in this case we still had quite intense residual sudomotor and vasomotor activity The case in which the sudomotor response was illustrated had a large amount of vasomotor activity in the foot In that particular instance therefore there was agreement between the vasomotor and the sudomotor data With regard to the other part of your comment as to the elimination of vasomotor activity by the extirpation of L2 and L3 we have many cases which have been referred to us in which that type of operation has been carried out and we have been able to demonstrate vasomotor reflexes without any difficulty at all Sometimes we found that the claimed operation had never been done despite the record and a statement by pathologists that ganglion cells had been found However we have not limited the operation to L2 and L3 I am not sure therefore whether the procedure of ganglionectomy of L2 and L3 would prove statistically satisfactory in securing vasomotor denervation And I am also not sure that vasomotor denervation is the whole story in some of these cases because we have several cases in which vasomotor denervation proved to be complete and sudomotor innervation still remained but the clinical result was unsatisfactory The picture is confused but we feel that the surgeon must do practically a total lumbar ganglionectomy in order to increase the incidence of therapeutic gains We have not done complete post operative follow ups on these cases so that we do not know yet what the full therapeutic results will be

BARCROFT A number of cases of lumbar ganglionectomy were performed in man by Mr Peter Martin by removing two lumbar ganglia. Mr Lynn wished to know how far the limbs were completely sympathectomized as judged by the plethysmograph technique in which the whole of the foot is enclosed. He examined—my guess would be—between 10 and 20 and in almost every case he found a complete failure to vasodilate when the body was warmed after operation. It does appear therefore *as far as the whole foot is concerned that the sympathetic cannot increase the flow through that part as a whole after the removal of these two ganglia*.

HERTZMAN So far our data apply only to skin and I think that is a most important distinction to make. The reflex vasodilatation test is uncertain evidence when it is negative unless one can carry through the test at different room temperatures. We found the test would fail often in a normal subject unless one provides a room temperature of 25 C or above. I should have no confidence in a negative result with room temperatures below 27 C to 28 C.

EDHOLM I think there is good evidence of a difference in response between North Americans and Britons. The normal indoor temperature (in winter) in North America is about 75 F (24 C) and in Britain it would only be 60 F to 65 F.

DORNHORST Dr Grant contrasted. I think the acetylcholine content of his muscular arteries according to whether they were sympathectomized or completely denervated?

GRANT No, the acetylcholine content goes with sympathectomy. It is the cholinesterase which is reduced to half by sympathectomy and abolished by total denervation.

DORNHORST Is there any contrast in the sensitivities and the effect of adrenaline in those which were denervated?

GRANT No. The increased sensitivity to adrenaline is produced by sympathectomy alone. I think sensory denervation makes no difference.

HERTZMAN I would like to correlate our observation that on the foot pad of the dog the threshold concentration of adrenaline injected intravenously is the same on the denervated as on the normally innervated side. However sensitization is demonstrable in terms of increased duration in intensity of response after one has passed the threshold dose.

GRANT I have no doubt that different animals vary. We have chosen *those two the rabbit ear and the human finger which show very close* parallels in other respects as well. They both have a rich supply of arterio venous anastomoses, they both serve not only local needs but general body needs in the regulation of body temperature and they have both up till now been supposed to be supplied by constrictor nerves only. Also in a rabbit the difference in sensitivity between a normal ear and a denervated ear to injections of adrenaline intravenously can be shown quite easily. One μg of adrenaline intravenously in the rabbit *will cause a gross constriction in the denervated ear* but have practically no effect upon the normal ear. I have done nothing with the dog—when you were comparing the normal and denervated dog's pad did

you have your dogs warmed so that the normal vessels were dilated too?

HERTZMAN We have done them both warm and cool

GRANT So that they had vasodilatation?

HERTZMAN Yes

GRANT I have no experience of the dog but I am confident in the rabbit and man The sympathectomized hand in man is more sensitive than the normal hand to injection of adrenaline

HERTZMAN The blood vessels of the dog footpad are exquisitely sensitive to adrenaline even in very low concentrations There are apparently *some dilator fibres that reach that area because stimulation of the* sympathetic trunk will sometimes result in dilatation But it is not marked and I do not think that the effects are important

GRANT That is rather different from the rabbit s ear and the human finger evidently because in them one cannot show any dilator effect by stimulation of the sympathetic fibres When the sympathetic nerves are cut there is full vasodilatation There is no increased sensitivity at once it takes several days to develop This must mean that acetylcholine is continually being released in the artery There is normally always a background of dilator effect going on on which the constrictor nerves work releasing adrenaline now and then so that constriction appears

WEDDELL Dr Hertzman s observations fit in very well with the results of dissections Sheehan has done much work on the location and development of these ganglia which is very relevant

LYNN *Dr Edholm has brought up the problem of North Americans* and Britons I was over in America some time ago and worked for a year in Cleveland in a constant temperature room and we did posterior tibial nerve blocks on American veterans from the Second World War who had had cold injuries I can remember offhand no patient—this was measured on a digital plethysmograph—in whom we could demonstrate a return of vasomotor tone in the toes after lumbar sympathectomy There might have been one but offhand I cannot remember any in 10 to 15 veterans in that study

HERTZMAN That is interesting because two weeks ago we had a case of an upper extremity sympathectomy but there was plenty of vasomotor activity in the hand

LYNN I quite agree that in the hand the situation is different

MARTIN It is a very different story in the foot in our experience *there is no return of vasomotor activity there This question of sweating* Dr Hertzman why is it that clinically about the second day when the blood flow is just past its greatest volume following sympathectomy you frequently get sweating of the hand for one day and then never again?

HERTZMAN I do not know

MARTIN On many occasions this has been observed by several people—I know Professor Telford of Manchester was interested in this point It occurs on the second day and after that you get a clinical anhydrosis

FITZGERALD I have seen it fairly frequently

HERTZMAN There may be irritation of the fibres

MARTIN Possibly but after that even on testing there is no apparent evidence of sweating later on

HERTZMAN Some of the colorimetric tests are not delicate enough to bring out residual sudomotor innervation The water may evaporate so fast that there is no opportunity for a colour reaction at all

GRANT I might suggest that there is one good way of showing sweating in the skin and that is to spread a smear of vaseline on the skin You can see the beads forming there and they persist since there is no chance for them to evaporate—even with minimal sweating

HERTZMAN Randall s sweat print technique appears to be more delicate than these other methods

VON EULER Dr Hertzman have you any experience with cases of so called postural hypotension? They are very queer in that they do not seem to have any functioning sympathetic system although I do not know if there is any histological evidence that this is so

HERTZMAN No we have no observations on it We have thought about it but we cannot get on to it

BURTON We found a fascinating problem many years ago we had a man who was a postural hypotensive and he had no vasomotor reflexes at all He was always fainting when he stood up and the blood flow in his fingers unlike the normal which fluctuates violently was quite constant He took a deep breath and nothing happened with a pin prick nothing happened to his finger flow And then in desperation we also studied the sudomotor system by the galvanic reflex There is a rhythm in the sudomotor system which is quite independent of the rhythm of vasoconstriction except when something startles the subject or when there is an exciting stimulus then both systems fire together To our astonishment this man had a perfectly normal psycho galvanic reflex a sudomotor reflex although he had no activity whatever in his vasomotor system Evidently the lesion was very much higher up in the C N S where the two systems are quite separate

VON EULER That is very interesting We have studied two cases which do not show any reaction in the urine at all All normal persons show a certain constant catechol amine excretion level unless they increase their work and so on but these cases show an extremely low excretion We have tried to stimulate their suprarenal by hypoglycæmia but they do not respond We have tried to provoke adrenaline secretion with histamine but obtained no response

BURTON In case you have not already discovered this I should like to give you a warning to be very cautious in these patients about injecting intravenous adrenaline because the effect is most devastating Since they have no buffer reflexes the blood pressure rises to fantastic heights and for a most alarming time

VON EULER We have tried that!

SOME ANATOMICAL OBSERVATIONS ON PERIPHERAL ISCHÆMIA IN MAN

J HENRY DIBLE

The problem of changes in the circulation and vasculature in limbs showing gangrene or local nutritional disorders attributable to the circulation has interested me for many years On the whole I think the pathology of peripheral vascular disease has been neglected and little has been added since the days of Rokitansky and Virchow if we except the coronary vessels on which a good deal of attention has been fixed The leg vessels and it is mainly in the legs that the condition I am speaking of arises are not a very attractive field for investigation The total length which must be examined makes it difficult and tiresome to get an accurate picture of the nature and extent of the disease whilst the amputation specimens are often offensive and uninviting A few transverse sections of vessels taken here and there tell us very little and I have found myself turning to the Hunterian method of injection dissection and naked eye and micro scopical examination Almost all my observations have been made on human amputated limbs and I have found an invaluable tool in arterial injection and radiography which of course can be more complete than *in vivo* These obser vations are on dead tissues and this limitation has to be constantly in mind in interpreting them

The points I wish to discuss in this paper are —

1 The causes of the vascular occlusion and the arterial pathology

2 The incidence and sites of occlusion

3 The effect of proximal vascular occlusions upon the more peripheral vessels

4 The special pathology of thromboangeitis obliterans

The pathological conditions are atherosclerosis and thromboangeitis obliterans These are distinct pathological entities though of course they can occur together since some degree of atherosclerosis is the usual accompaniment of ageing and may be found in people in the thirties

Atherosclerosis

Atherosclerosis is a compound of at least two apparently independent processes—Monckeberg s medial calcification and atheroma—and it is to some extent allied to the other two changes which age brings to the arteries, viz medial fibrosis and thickening of the endarterial layer The pathological process in this disease is one of thickening of the intima which in vessels such as the femoral and to a lesser degree the popliteal may be markedly of the eccentric sub intimal fatty cholesterol type so frequently seen in the aorta In the three main leg arteries however it is a more uniform though generally also eccentric layered fibrous hyperplasia composed of a loose fibrous and often œdematous acellular and avascular tissue which surrounds narrows and finally obstructs the lumen The central occluding tissue is often soft and gelatinous and when the occlusion is complete may be seen by the naked eye as a greyish avascular plug Endarteritic overgrowth may either itself occlude the lumen or final complete occlusion may be brought about by complementing thrombosis It is often very difficult to say which of these processes is responsible for the final occlusion or the extent to which they are combined I think from the evidence of my own specimens that in the leg arteries occlusion is mainly due to atheroma if we may extend and apply this word to the special fibrous intimal change which occurs in the peripheral arteries as the counterpart of typical atheroma in the larger more central vessels But whatever its distribution and whatever part thrombosis plays in providing the final occlusion the disease always bears the hall mark of a degenerative change One important point is that this disease is extremely patchy I do not mean that stretches of diseased

vessel in general alternate with stretches of perfectly healthy vessel it is more usual for the vessel to be more or less diseased over long stretches perhaps from its origin to as far distal as where the leg vessels give way to the foot vessels But the disease is patchily intensified so that the X ray picture of the injected vessels may show marked irregularity of outline the lumen when patent being constantly constricted at irregular intervals throughout this whole length

The next point is that this occlusive disease in the cases in which it leads to amputation almost always involves the complete obliteration of one or more of the main leg arteries at some point or another My figures for complete obliteration in 34 cases on the basis of there being four main arteries to consider viz Femoral Popliteal Anterior Tibial Posterior Tibial and Peroneal are 6 per cent of cases 1 artery only obliterated 45 per cent 2 arteries obliterated 36 per cent 3 arteries obliterated 15 per cent all 4 arteries obliterated

When we turn to the way in which the obliterative disease falls upon the different arteries we find the distribution shown in the table —

INCIDENCE OF CHRONIC OBSTRUCTIVE ATHEROSCLEROTIC LESIONS IN VESSEL OF THE LOWER LIMB IN CASES OF AMPUTATION FOR ISCHÆMIA OR GANGRENE (per cent)

	Femoral	Popliteal	Ant. Tib.	Post. Tib.	Peroneal	Dorsalis Pedis	Ext. Plantar	Int. Plantar	Digital
Obstructed	24	43	87	79	45	19	19	15	0
Partially obstructed	33	23	3	9	12	6	4	0	27
Patent	43	33	9	12	35	5	77	85	73

It is to be remarked that the proportion of obstructive lesions in the main arteries is reversed in those of the foot the peroneal occupies an intermediate position I shall describe two examples to illustrate the effects of obstruction of the major arteries which differ extremely in their details

Case II 73 was one of extreme claudication with no pulses palpable in the femoral posterior tibial or dorsalis pedis

amputation was performed by Mr Martin for pain and trophic ulceration At the amputation site there was complete obliteration of the femoral and popliteal trunks of long standing Injection could however be made through the posterior tibial which was patent at the ankle and this showed good patency of all three leg vessels There was no patency of the popliteal the blood reaching the leg mainly through an enlarged *arteria comes nervi ischiadici* Lower down the dorsalis pedis was obstructed by atherosclerotic endarteritis but the plantar vessels were capable of being well filled *via* the posterior tibial (Fig 1)

I could multiply such examples and show you different combinations of ischæmic and patent vessels but I shall only quote one other case

Case W 55 At the opposite extreme we have an example in a diabetic patient of 69 who had gangrene of the great toe and much pain The politeal vessel was patent and injection of the limb through this showed a complete absence of all the main arterial trunks of the lower limb only a stretch of the lower peroneal being identifiable on the radiogram but the foot vasculature was remarkably well preserved (Fig 2)

Until I took up this study I certainly did not appreciate how utterly distorted the normal vascular pattern can become and yet be compatible with reasonable function for a long time Blood may start from the popliteal switch to the peroneal track by it to the ankle region and pass thence by passing an obliterated posterior tibial into the two plantars then by way of the tarsal arch run back into the dorsalis pedis and fill the lower part of an anterior tibial which is obliterated throughout the greater part of the leg

This brings me to my third point that the vessels of the foot suffer far less than do the more proximal trunks and their condition is more often than not excellent—as can be shown by injection through a patent distal vessel such as the dorsalis pedis or the posterior tibial at the ankle Not only in atherosclerotic limbs is there frequently an abundant potential vascular supply for the foot but the normal dispo



Fig. 1 (Case W 73). Showing good vascular supply to the foot, the vessels being filled via the posterior tibial.



FIG. 2 (Case W. 55). Atherosclerotic obliteration of the three main leg arteries. Good vascular pattern in the foot by minor anastomoses.

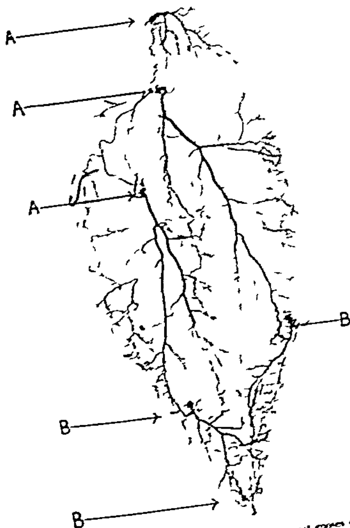


Fig. 3 (Case W 71). Shows the superficial anastomoses of the upper and lower arteries to the soleus muscle.

of the posterior tibial injection into this vessel from below showed that the path of least resistance to the popliteal artery was *via* the anastomoses of the superficial muscular branches of the gastrocnemius arteries it being quite easy to fill the popliteal vessel without filling the muscle capillaries (Fig 4)

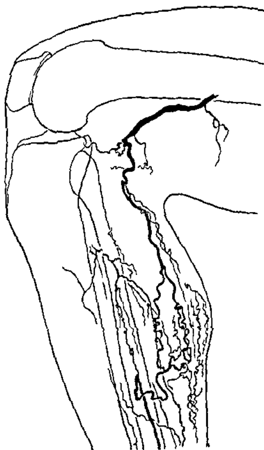


FIG 4 (Case VIII) Tracing of arteriogram showing anastomoses of popliteal and posterior tibial vessels by way of the superficial anastomoses of the arteries to the gastrocnemius muscle

Thromboangeitis Obliterans

I believe it is now suggested in some quarters that this is not a disease in its own right but is the same as athero sclerosis I am not concerned to deal with the clinical differ ences between these two but I would say that the pathological differences are profound Whereas degenerative and avascular lesions in the vessels are the changes typical of atherosclerosis cellular vascular and formative lesions are those of throm boangeitis The picture here is quite unlike the eccentric degenerative occluding tissue characteristic of the former disease

I do not think the extreme vascularity of the affected arterial wall and the adjacent perivascular fibrous tissues can be appreciated unless one studies injected specimens Furthermore the disease has a much greater predilection for the small vessels such as the digitals which usually escape in atherosclerosis and this results in a profound disorganization of the functional vascular tree It is difficult to get good X ray pictures from these cases because in my experience they are generally operated upon piecemeal over a long period and when a whole limb is obtained the arteries are so altered that it is physically difficult to make a satisfactory injection I have seen in the foot arteries complete disorganization of the normal pattern which is so strikingly maintained in atherosclerosis The main channels are lost and replaced by a host of smaller vessels I quote and illustrate (Fig 5) the case of a young Pole—aged 25—whose leg was amputated below the knee by Mr Martin his vessels show the typical picture of thrombosis followed by extensive recanalization with the development of leashes of small vascular channels Such wide chronic thrombosis and revascularization is most unusual (I cannot recall it at all) in atherosclerosis Venous involvement in this disease is common it is rare in atherosclerosis

DISCUSSION

DAWES I am not quite sure whether the anastomoses that you showed would really account for the proposition put forward by Dr Dornhorst because it seems to me that these were really arterio arterial anastomoses *in abnormal limbs whereas what he is looking for are surely AV* anastomoses in the normal limb Might it not be that the arterio *arterial anastomoses which you see in these diseased limbs are greater* in amount than you would see in the normal limb?

DIBLE Yes I think they probably are greater unfortunately I have not done a sufficient number of controls to be able to say to what extent they are present in the normal limb But I think that there must be a pressure gradient between the vessels which arise from a large artery (for example the posterior tibial which fills the upper part of the soleus muscle) and those which come from a small artery (for example the peroneal) so that there is a possible by pass through this system We are rather too apt to be dominated by the idea of a single trunk entering into a part and splitting up into its tributaries which are then gathered up into the veins than by the real arrangement which is a series of arterial arcades of different sizes and at different levels It is surely possible under physiological conditions for some of these to be shut off by influences which you know all about (I know nothing about them) *and for the blood to circulate through the main trunks rather than* through the capillary circulation in the depths of the muscles

WEDDELL We have made a number of injections in stillborn material and they confirm what Dr Dible has said in relation to the adult The anastomoses are common and they give pictures which look very much like those shown by Dr Dible

DORNHORST I think in considering the anatomy of the collateral circulation one has to remember that Professor Dible s material has a bias—it is the unsuccessful collateral circulation that he is examining This is not a quibble because arteriography does show that this type of picture of the complicated net does indicate a bad prognosis on the whole and that the limbs which escape amputation for a few years have fewer and larger collateral vessels

DIBLE On that point I would say unsuccessful at the time that *the operation was performed but successful for a good many years* previously

FITZGERALD There is a rather distinct difference between an arterio*gram in a living individual and a cadaveric arteriogram.* I think most people who deal with them both in the surgical and in the anatomical field will realize that there is a rather profound difference between the degree of network formation which is found in the dead subject and the living Whether it is indeed due to the fact that there is a release of tone or something of that nature I really do not know but there is a distinct change

DIBLE I agree absolutely with that but what the cadaveric arteriograms show are the potential channels

MARTIN We have some arteriograms prior to death and some from

limbs which have been amputated The picture is of course entirely different but I think Professor Dible puts in his radio opaque material at a fairly high pressure—much more than we would ever use in an arteriogram in fact we do not use any added pressure at all Professor Dible's method achieves the object of his exercise

DIBLE Yes that is true I put it in at the highest pressure I can short of bursting the artery but the object of the exercise is to show what the channels are or what the potentialities are

FITZGERALD There is another small point in relation to the position of the arterial pattern in these cases I wonder would Professor Dible confirm it or otherwise? If one amputate the legs as is usually done without a tourniquet I get the impression that you find small bleeding points in relation to the section of the muscle immediately deep to the surface of the muscle and not in the centre of the muscle at all These bleeding points are not exactly arterial in the sense that they spurt yet at the same time they contain blood which obviously is not venous It is under low pressure but it is considerably above that of venous blood

MARTIN Do you maintain Professor Dible that the main collaterals are in the intramuscular spaces rather than in the muscles themselves or do you think there are important collateral vessels which come through the muscles?

DIBLE The main collaterals are in the intermuscular spaces but what I was trying to demonstrate is that there can be collaterals through muscles and I think I would agree (without being certain about this) that they are not very deep in the muscle They are in the superficial layer of muscle but they are muscular and not extramuscular

BURTON Would you say something about what you see in the arteriosclerotic limb? You have shown us that the vasculature of the foot is usually very good but is supplied through long channels which may mean it has lower blood pressure What did you see in the smaller vessels for example the arterioles of the digits? Are we to think that the ischæmia is due merely to the fact that the good vasculature of the foot is now filled under a lower pressure or is there a disease process in the small vessels in the digits of that foot?

DIBLE The vessels of the small digits are generally healthy I think it is entirely a question of stagnant circulation due to blood being supplied at a low pressure

NICKERSON It is interesting that there is some statistical evidence that certain vessels are predisposed to clotting I am wondering if possibly it might be due to a dynamical situation where a long vessel has two arterial supplies—one above the level of clotting and one below so that the pressure gradient and hence the flow in that area would be reduced The blood might tend therefore to stagnate and hence form clots in that region

DIBLE I cannot answer that

MARTIN There is considerable evidence that the common points of thrombosis in a main artery are at the junction of a relatively fixed segment of artery with a relatively free segment of artery The popliteal artery as it passes behind the knee joint goes between the layers of the

posterior ligament of the knee joint where it is firmly fixed and just above this it is in the fibro fatty tissue of the popliteal fossa where it is relatively free and at this site thrombosis is frequently seen The same occurs in the opening of the adductor magnus through which the femoral artery passes

ALGIRE What is the source of the new vessels Professor Dible in the recanalization?

DIBLE I think inside the internal elastic lamina they are formed by endothelium *from the vessel above and possibly from undifferentiated* histiocytes What is so striking is that there seems so very little anastomosis between the large vessels outside the lamina and the vessels which you find inside The anastomoses seem to run up and down inside the lamina they do not seem to come in and follow a contorted course through the clot In all these transverse sections this was what I found

GRANT I think I would agree with that I have followed in serial sections the recanalization of the thrombi and they do it from end to end and not from side to side as was once thought

VON EULER What do the vasa vasorum look like in these diseased parts? Do they show changes of the same kind?

DIBLE The vasa vasorum do not show pathological changes at all

BURCH Were the vasa vasorum derived from the vessels outside the thrombosed one?

DIBLE Yes the true vasa vasorum are derived from another artery

BURCH Could disease of the vessels outside the thrombosed one have first interfered with the circulation of the wall of the vessel which in *turn might have produced the disease which led to a thrombus?*

DIBLE Yes theoretically but then one does not find it

FITZGERALD Do you ever find a serous fluid separation between the clot and the internal elastic lamina?

DIBLE Yes particularly at the upper parts of the clot a space perhaps It is always called retraction but whether it is retraction or not I don t know *A space does develop and it becomes endothelial* lined very rapidly

FITZGERALD Do you find any signs of that near the centre of the clotted region?

DIBLE Yes you may do but chiefly in short clots I do not think you would find it in large ones

BURTON I would like to draw attention to the unfortunate physics of the atherosclerotic situation in large vessels It has been taken up eagerly by Dr Paterson in our university and by other pathologists interested in the problem This is the Bernoulli theorem—that once you begin to get the beginnings of an obstruction (an atherosclerotic plaque in a vessel) and you have a narrow cross section there blood has to flow very rapidly through that narrow segment which means that the side pressure is very much lower (this is the principle of the filter pump) Therefore the narrower it gets the greater is the tendency for the vessel to close down In fact the side pressure may become lower than atmospheric pressure Moreover this may play a big part in the

formation of thrombi in that the clot has blind capillaries coming from the sides where the pressure is still quite high much higher than the pressure on the tissue of the plaque This creates a most unstable situation because one can well understand how these capillaries that have grown into the plaque break and the thrombus then breaks off It all goes back to the problem that was tackled by Lord Kelvin when he was an undergraduate in Glasgow—the problem of steering a boat in a small canal a problem due to Bernoulli s theorem I think this really plays a very big part and shows how once you begin to get an *obstruction in a large artery the thing becomes self propagating so to* speak and the physics of it is most unfavourable

DORNHORST Did you calculate the forces involved? They are very small compared with the blood pressure swings

BURTON I disagree with you quite violently on that!

DIBLE A real difficulty in that theory is the extraordinary avascular condition of the atheromatous plaque One of the striking things about it is how with so few vessels it manages to survive at all

GUTTMAN Could you tell us something about the acute changes in the vascular system in the acute stages of ischæmia occurring say due to pressure and leading to pressure sores? There is surprisingly little in the literature

DIBLE No that is outside my field I cannot tell you anything first hand about that A man in Cameron s laboratory at University College Hospital has been working on the problem of the pressure sore

HOWARD There is a certain amount of evidence on the effects of occluding the vessel completely by pressure Sharpey Schafer has done it I think.

DORNHORST Yes I am not quite certain of Dr Guttman s point Are you interested in the effects of pressure on the main vessel or pressure on the cutaneous vessels?

GUTTMAN On all On main and on cutaneous and subcutaneous vessels

DORNHORST Well as far as acute occlusion of the main goes one can show that there is some dilatation of the collaterals starting within a minute That continues for several minutes and we imagine it goes on steadily fast at first and then less fast for a considerable time probably *for several weeks This I am sure accounts for the main part of the* striking change which occurs in the first few hours after for example an embolus or an arterial ligation One of the physiological problems in this is what is the stimulus for that opening of collateral vessels? I think that if we knew that it would be quite important

HOWARD Was that work only done on the upper limb or did you do some on the lower limb too?

DORNHORST We only did it on the upper limb but Shepherd did it on the lower limb with a large compression pad on the femoral artery

HOWARD I wondered whether that might tie in with Dr Edholm s point that this ischæmic business is much more common in the lower limb whether in the upper limb there are more anastomoses existing normally

DORNHORST I think there is more atheroma in the lower limb—that is I suggest the fundamental difference—and that is because the lower limb has chronic hypertension unless we stand on our heads!

FDHOLM There is one interesting point I have never seen described before and that is the remarkable vascularity of the heel Is that a constant finding in these arteriograms?

DIBLL Yes and I suppose it has to be otherwise it would go gangrenous

MARTIN I do not know if anybody has done any anatomical studies on the blood supply of the heel but in a normal arteriogram a large number of arterial arcades arise from the posterior tibial artery as it

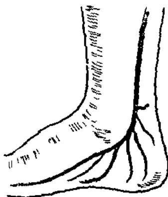


FIG 1 (Martin)

passes behind and below the median malleolus These run directly to the skin over the heel giving rise to a very efficient blood supply in this area (Fig 1) These are important clinically because if they are not apparent then the blood supply of the heel is severely limited and the heel could easily become gangrenous

GUTTMAN I think this is a very important statement regarding the development of sores over the heels in paraplegic patients Having regard to the anatomical arrangement of the vascular supply of the heels it is obvious why rings of rubber etc used as a rule to prevent pressure sores over the heels are not only not satisfactory but may be even an excellent means of producing ischæmia and sores.

THE MECHANISM OF THE RAYNAUD S PHENOMENON IN PATIENTS WITH HIGH SERUM TITRES OF COLD AGGLUTININS

J T SHEPHERD

PATIENTS whose serum contains cold agglutinins in high titre are unusually liable to develop numbness and cyanosis of the digits and other parts on exposure to local cold

We have examined the peripheral vascular responses in two patients with a high serum titre of cold agglutinins not associated with any other disease (Marshall Shepherd and Thompson 1953) The clinical and hæmatological findings have been described by Nelson and Marshall (1953) Our object was to determine whether the attacks of the Raynaud s phenomenon in these patients is solely the result of blockage of vessels by agglutinated red cells or whether an associated vasospastic condition plays a main or contributory part in reducing the blood flow (Carey Wilson and Tamerin 1948 Kramer and Perilstein 1951)

We believe that the attacks of numbness and cyanosis can be explained by mechanical obstruction of the vessels by agglutinated red cells and that it is unnecessary to postulate that the vessels themselves behave abnormally The evidence for this contention depends on a comparison of these two patients with patients suffering from a known vasospastic disorder namely Raynaud s disease (Lewis 1930a) The difference in the circulatory response in these two conditions has been demonstrated in the following ways —

(a) The blood flow through the hands was measured by venous occlusion plethysmography Indirect heating to re lease sympathetic tone in the hands (Lewis and Pickering 1931) was carried out by immersing the feet and legs in a stirred water bath at 42 44 C and wrapping the subject in

blankets (Gibbon and Landis 1932) The circulation to both hands was then arrested and one hand exposed to water at 10 C On release of the circulation ten to fifteen minutes later there was practically no flow through the cooled hand of the patients with high cold agglutinin titres while in the patients suffering from Raynaud s disease there was a high flow through the cooled hand

(b) The heat loss from the distal 2 8 cm of one finger tip to water at 0–2 C was measured by a calorimetric method (Greenfield and Shepherd 1950) In normal people there is an initial decrease in heat elimination after insertion of the finger into cold water due to vasoconstriction This is followed in five to ten minutes by a vasodilatation and hence by a large increase in heat loss due to an increased blood flow through the part This vasodilator response of the finger vessels to cold was originally described by Lewis (1930b) In one of the patients with a high titre of cold agglutinins there was no increase in blood flow through the finger even after forty minutes immersion in the cold water whereas patients with Raynaud s disease almost invariably have a large increase in flow (Thompson 1952)

(c) When the hands of the patients with the cold agglutinins were cold and cyanosed intermittent pressure on the cyanosed areas failed to produce temporary pallor (Hanns 1943) as it does in the cyanotic episodes of Raynaud s disease

(d) During recovery from an episode of cyanosis the ulnar border of one finger of one of the patients with cold agglutinins suddenly became red while the radial side was still deeply cyanosed This unilateral flushing has not been described during recovery from attacks of Raynaud s disease

The above results can be adequately explained by intravascular blockage of vessels by agglutinated red cells Under ordinary conditions of exposure to cold however normal vasoconstriction will be an additional factor tending to reduce the flow This view has been postulated by Stats and Wasserman (1943) and Forbes (1947) but to our knowledge has not previously been demonstrated

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DISCUSSION

GRANT There is one very interesting point which I would like to advance further This is that you attributed the vascular obstruction to mechanical blocking I understand Have you considered the possibility of a vasoconstrictor substance being released during the agglutination of the cell ? It is very easy when handling blood to produce vasoconstrictor substances and I was wondering if you had any evidence for or against the possibility of a vasoconstrictor substance in the cool part I think mechanical blockage would be difficult because of the ease with which emboli and various things pass through the vessels in the finger

SHEPHERD There may be but I have no evidence

EDHOLM How quickly is the circulation released when the cold hand is put into warm water?

SHEPHERD If you put the cyanosed hand into hot water there is very rapid reddening of the whole hand and when you put it into cold water again the cyanosis reappears

EDHOLM That would support the mechanical theory of obstruction

HERTZMAN I would like to emphasize the possibility of vasospasm Contrary to Dr Shepherd s strong evidence I have seen in peripheral vascular cases complete independence of vasomotor activity in neighbouring fingers One may see a constriction in one while another is dilating It is rather a weird phenomenon One wonders whether it is a local vascular phenomenon or is being mediated by vasomotor fibres The latter possibility exists in cases of irritative lesions in the sympathetic ganglia with resultant highly localized vasomotor effects it is quite possible that facilitation may appear when thermosensory information comes in That would trigger off the irritative pathways I have often wondered whether that possibility is realized I can think of no other explanation for such phenomena

SHEPHERD If there is a vasospastic element in these people with high cold agglutinin titres their vessels must be even more sensitive to local cold than people with Raynaud s disease That is a possibility but I think it is a very unlikely one

DORNHORST The part of Dr Shepherd s observations which fascinates me is the demonstration of normal hunting reactions of the arteries in Raynaud s disease I find very extraordinary these very high rates of elimination—he told us that they implied very high flows—and that seems to suggest that the whole of the digital artery must be relaxed I think this throws doubt on the whole concept of Raynaud s disease as a local hypersensitivity to cold

GREENFIELD Dr Thompson made an extensive survey of Raynaud s disease and I think he has found practically normal responses to cold in every case which he has examined except one

EDHOLM *That is response to extreme cold*

GREENFIELD Yes between 0 and 6 C

GRANT You would not expect to get the full vasoconstriction if the body was kept warm You had indirect heating Dr Shepherd did you not?

SHEPHERD Yes during the plethysmographic experiments but the calorimetric experiments were carried out in a warm room without indirect heating

DORNHORST I am wondering how much of the artery is involved In a Raynaud s attack the whole finger will change colour and it very much suggests that a considerable length of the digital artery is involved And by local extreme cooling of the tip one gets very high flows producing somehow an unconstricted base of the artery Would you agree with that? It seems to me a strange thing and worth looking into in more detail

GREENFIELD Dr Thompson has found it rather difficult to produce attacks of Raynaud s disease although in all his cases he has seen attacks which came on spontaneously They happened to arrive with an attack but it is quite difficult even by putting them into water at 10 or 15 C or indeed at any temperature to induce an attack at will

DORNHORST You cannot abort or terminate an attack of Raynaud s by putting the hand in ice

FITZGERALD I think clinically the same difficulty arises Usually if you get the patient to go out and walk around they get the attack It is rather a peculiar thing how the combination of exercise and exposure to very moderate degrees of cold does produce it while immersion of the hand in iced water will not bring on the attack. Another thing which Dr Grant mentioned which I have also seen is the unilateral disappearance of Raynaud s along a digit Indeed you occasionally see it I think in acrocyanosis which is a very much less pronounced type of vasospasm.

HERTZMAN Another point to be emphasized is the important position of sympathetic ganglia in these peripheral vascular cases It is necessary to distinguish sharply between some local sensitivity to cold through this normal mechanism and the possible exaggeration of a normal vaso-

motor reflex which might have a fairly sharply defined locus of action Dr Kuntz has examined many ganglia taken out from peripheral vascular cases and I think I am correct in saying that he has not yet seen a normal sympathetic ganglion in these peripheral vascular cases Maybe the lesions in the ganglia are the basis for the peculiar vasomotor picture or maybe the peripheral vascular di ease is not limited to the periphery but also involves part of the ganglia

MARTIN Lériche pointed that out some time ago didn t he? A large number of stellate ganglia from patients with and without vascular disorders were examined and exactly the same pathology was found in those without and with vascular disease

GREENFIELD On the general principal of economy of hypotheses I should have thought it was unnecessary to postulate a ganglionic involvement to explain Dr Shepherd s results

EDHOLM I would like to bring the discussion back to cold agglutinins Could Dr Shepherd tell us at what temperature agglutination occurs?

SHEPHERD Well it varies Some people have a very high titre at 0 C which decreases sharply as the blood is warmed Others may have a lower titre at 0 C but this may only decrease slightly up to 20 C or even higher This probably accounts for some of the apparent discrepancies in the literature where cases have been described with very high cold agglutinin titres without symptoms directly referable to hæmagglutination It is obviously important to measure the titre over a wide temperature range as the thermal amplitude of the antibody is an important factor is determining the occurrence of symptoms

EDHOLM Is this a common condition?

SHEPHERD There have been quite a few cases described but most of them have been associated with virus pneumonia and some other rarer conditions With these there is a transient rise in titre at the height of the illness or just after the illness but in the two cases I have described the high titre has persisted over a long period without any other obvious pathology

VON EULER Would this plugging up of the vessels occur in other parts of the body too? Is it a general phenomenon?

SHEPHERD Yes it is You get it in ears nose hand and feet and in fact in any exposed parts

VON EULER From the mechanical point of view is there real evidence that this agglutination does cause a block?

DORNHORST I think you can see it quite clearly in the conjunctival vessels

BARCROFT *It would be rather interesting to try producing it in* another part of the body by cooling that part say the forearm skin

SHEPHERD That is the basis of one of the tests for this condition The arm is immersed in water at about 12 C for about twenty minutes and this is often followed by hæmoglobinæmia and occasionally by hæmoglobinuria The same may happen on a cold day

DAWES Is there any evidence of what happens to the platelets when agglutination takes place?

SHEPHERD I do not know of any but there may be

DAWES Is there a possibility that 5 hydroxytryptamine release has been completely excluded?

SHEPHERD No I do not think so

VON EULER If you cocainize your vessels do you get the plugging? In such a case they would not react to any vasomotor substance which was *circulating or to any indirect vasoconstrictor substances*

SHEPHERD Again I cannot say For the plethysmographic observations we had a control hand in water at 32 C and for the calorimetric experiments we had a control finger tip in a calorimeter at 30 C During the period when the opposite hand or finger tip was cooled there was no decrease in blood flow through the control side Of course any vaso constrictor substance which may have been liberated may not have been in sufficient concentration or may have been destroyed before reaching the other side

DORNHORST In this condition if you take blood in a test tube and just put it under a cold water tap it becomes like coffee grounds It is really no surprise that it does not go very nicely through vessels It is astonishing how everyone wants vasoconstriction and vasospasm isn t it?

DAWES No I don t think so I think that if the blood becomes like coffee grounds it might be well worthwhile investigating it to see if something is released I do not see that because the facts can be explained by one mechanism that necessarily precludes the possibility of another one perhaps working the same way and reinforcing it

SHEPHERD If you cool the blood in a test tube there is almost spontaneous agglutination but there is quite a lag between agglutination and destruction of the cells

KERSLAKE If you heat it up again does it go back to its unagglutinated state?

SHEPHERD Yes very rapidly With regard to the liberation of vaso constrictor substances in the blood we find with intra arterial infusions that if you withdraw some blood into a syringe for a few seconds and then put the blood back into the artery there is a vasodilatation and not a vasoconstriction

GRANT You get a mixture don t you? In my experience in man and the rabbit you get mainly a vasoconstriction It is very difficult to get a sample of blood free from these vasoactive substances

GREENFIELD In relation to the question Dr Grant has raised as to how the finger vessels through which normally quite large things will go get blocked by agglutinated cells is it not probable that when exposed to cold the vessels just constrict in the normal way and then become blocked?

SHEPHERD Yes we believe that under ordinary conditions when these patients are exposed to cold there is a combination of vasoconstriction plus blockage by agglutinated red cells but no vasospasm We are not saying that these vessels don t constrict The point is that the attacks of Raynaud s phenomenon in these patients are not the result of any abnormality of the vessels themselves

COOPER Perhaps we might expect the vessels to clamp down If you

have some clumps of red cells partially obstructing the flow the pressure distal to the obstruction would drop and then (as Professor Burton would tell us) the critical closing pressure might be reached the vessel would collapse and then would occur a condition of complete blocking

BURTON What is the incidence of this condition? It is my impression — Dr Burch and Dr Hertzman will back me up in this—that we seldom get a chance to see this do we in the United States or Canada? I don t think it exists in North America

EDHOLM There have been several papers from the States on the incidence of cold agglutination It is certainly not unknown there

CARLSON The reports on cold hæmagglutinins are probably not all in the general literature Fort Knox reports are published as U S Army Medical Research Lab reports Fort Knox Kentucky

MARTIN They have one interesting report from there—I think—showing that those soldiers in Korea with high titres of cold hæmagglutinins are more liable to frostbite

EDHOLM Investigations are going on on that very point

ASMUSSEN I would like to ask if this reaction to cold would have anything to do with the fact that some persons by swimming in cold water get cramps first?

EDHOLM On the contrary there are a number who may get cramp on swimming in cold water but do not have a high titre of cold hæmagglutinins

VISCERAL ACTIVITY AND PERIPHERAL CIRCULATION IN THE SPINAL MAN

L GUTTMANN

IN this communication I propose to give a short survey of systematic studies on the effects of visceral distension especially distension of the bladder on autonomic mechanisms in the spinal man which I have undertaken with my co workers since 1944 Emphasis is laid on the effects on peripheral circulation and attention is drawn particularly to a vasodilator response as an adaptive regulatory mechanism

There are only scanty references in the previous literature to vasomotor reactions in response to the distension of the urethra or bladder in complete lesions of the spinal cord in man Bowley (1890) mentioned a boy of 18 with a fracture dislocation of the 7th cervical and 1st thoracic vertebræ resulting in a complete crush lesion of the cervical cord with tetraplegia who showed profuse sweating over the head face and neck and the development of a bright red rash, when a catheter was passed persisting for fifteen to twenty minutes Head and Riddoch in 1917 in their classical study of paraplegics from World War I mentioned a case of transection of the mid thoracic cord who to the amazement of the investigators complained of head fullness when the bladder was distended

However in recent years experimental studies on animals and normal man have shown that the distension of abdominal viscera evokes widespread reactions on autonomic mechanisms

The immediate cause of my own study was the following observation On the occasion of cystometrographic examination in April 1944 on three patients with complete lesions of the upper thoracic cord (T 3 T 4 and T 5) distension of the



Fig 1 Complete lesion below T 1 Reflex sweating due to vesical activity involving head neck both arms upper trunk and diminishing towards T 10 Complete anhidrosis below T 10 Anhidrotic area of the left upper arm is due to blood pressure cuff worn during the experiment



A



B

Fig. 2 A, B. Complete lesion below T 4. Reflex sweating at the level of the lesion elicited by distension of the bladder. Dark lines illustrate distribution of vasodilatation in face and neck at the height of vesical activity. (From L. Guttmann and D. Whitteridge, *Brain*, 1947, 70, 361.)



A



B



C

Fig. 3 A, B and C. Complete lesion below T 5. Reflex sweating and its distribution during bladder distension. Sweating starts at the level of the lesion, more on the left side than on the right; in later stages sweating spreads to T 11, and in final stage involves also the inner side of both arms and the whole of both hands.

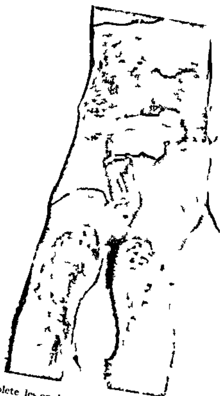


Fig 5 Complete lesion below T [illegible] Reflex sweating due to bladder distension In contrast to the reflex sweating in high thoracic and cervical lesion in mid thoracic lesion it involves the lower part of the body (below T 5 6) and in this particular case there is an especially profuse band like hyperhidrosis between T 10 and T 11 on the right and between T 10 and T 12 on the left side indicating a state of distinct hyperactivity of these segments situated below the level of the lesion.

obtained on the peripheral circulation can be summarized as follows Distension of the bladder in all complete lesions of the spinal cord sets up reflex responses of the cardiovascular system which are dependent in consistency and intensity on

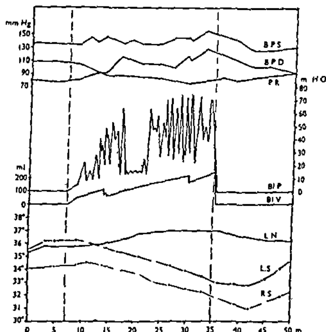


Fig 4 Complete lesion of the spinal cord below T 8 Bladder distension in correlation to bladder volume (Bl V) bladder pressure (Bl P) systolic blood pressure (B P S) diastolic blood pressure (B P D) pulse rate (P R) and skin temperature above and below the level of the lesion L S =sole of the left foot R S =sole of the right foot L N =left side of neck (From L Guttman and D Whitteridge *Brain* 1947 70 361)

the level of the lesion as well as local condition of the bladder *The basic reflex response to bladder distension in all complete* lesions above L 2 with intact isolated cord is vasoconstriction in the lower limbs especially the toes which is not limited to the skin and is mediated by the lowest part of the sympathetic outflow Since in these low lesions *there are large*

areas of the vascular bed left which can be utilized for vaso motor regulation the vasomotor adaptation response to the vasoconstriction in the lower limbs is vasodilatation in parts above the level of the lesion especially the fingers It may be noted that in distal lesions of the spinal cord the increase of bloodflow occurring in the upper limbs as a readaptation response to its decrease in the lower limbs also involves the vascular bed of the muscles Skin temperature measurements showed a fall in the area of vasoconstriction especially the toes while there was a rise in the upper part of the body especially in the head No changes of blood pressure were found in paraplegics with low thoracic cord lesions (Figs 4 and 5) while those with lesions of the mid thoracic cord showed only an insignificant rise Sweating in mid thoracic lesions elicited by bladder distension involves the lower part of the body but certain segments which may be in a state of hyperactivity caused by irritation from the post traumatic changes may show particularly marked hyperhidrosis as shown in Fig 5

In spinal transections at or above T 5/6 however where the whole splanchnic outflow is situated below the level of the lesion conditions are quite different In these cases vaso constriction in the toes due to visceral distension is accom panied by vasoconstriction also in the fingers and a steep fall in pulse volume in toes and fingers occurs (Fig 6) There is a very large rise in blood pressure both systolic and diastolic The pulse rate shows a marked drop and changes of rhythm are noted and the electrocardiogram may show increase in the size of the U waves (Fig 7) These findings indicate that an increase in the load on the heart must occur at the height of bladder activity due to distension and this was proved by X ray studies of the chest in correlation to cystometrograms It was found that at the height of visceral activity in upper thoracic and cervical lesions the heart shadow may show an increase by several centimetres (Fig 8) However even in these high lesions an adaptive vasodilator mechanism is mobilized to counteract the effects of vasoconstriction of even

so large an area of the vascular bed There is a marked vaso dilatation in the upper trunk, shoulders face and neck of patchy type, associated with congestion of the naso pharyngeal mucosa resulting in blockage of the nasal air passage

When in lesions at T 1 or C 7 the bloodflow was measured it was found that while in the fingers vasoconstriction was so

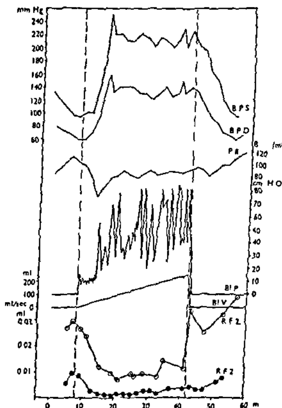


FIG 6 Complete lesion below T 2 3 Effect of distension of the bladder on the blood flow through a finger in a patient with a high lesion. B P S systolic blood pressure B P D diastolic blood pressure P R pulse rate Bl P bladder pressure Bl V bladder volume R F 2 — — pulse volume in right index finger (From L Guttmann and D Whitteridge Brain 1947 70 361)

prevalent that the bloodflow through the vascular bed of the skin to the fingers almost ceased the bloodflow in the vascular bed of the muscles of the forearm was greatly increased and

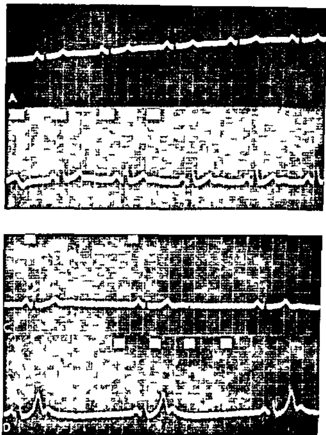


FIG. 7. Complete lesion below T 8. Electrocardiograms before (A and B) and during (C and D) distension of the bladder in a patient with a high lesion. A and C lead II, B and D lead IVR. Notice the slowing of the heart rate and the increase in size of the U wave especially in lead IVR. (From L. Guttmann and D. Whitteridge, *Brain*, 1947, 70, 361.)

the head also showed definite signs of vasodilatation These are very remarkable findings which are not in accordance with accepted views regarding vasomotor innervation In these high lesions as far as the sympathetic innervation is concerned not only the fingers but the whole of the upper limbs face and neck are situated below the level of the lesion Therefore one would expect vasoconstriction during visceral distension not only in the fingers but also in the whole of the upper limbs face and neck—the more so as profuse sweating occurs in face neck arms and chest (Fig 1) However face neck and arms show marked vasodilatation

The mechanisms involved in this vasodilator effect in high lesions of the cord are by no means obvious and various possibilities have therefore to be analysed

Vasodilatation of face ears and neck and nasal congestion could be the result of paralysis of vasoconstrictor nerves since it occurs as a regular and immediate result of cervical sympathectomy as well as in the acute stage following transection of the cervical cord However there is no evidence that the vasodilatation in face neck ears upper chest and arms, set up by bladder distension in these high lesions of the cord is due to paralytic vasodilatation, as there is every sign of increased sympathetic activity On the other hand if in these cord lesions, the vessels in face neck upper chest and upper arms are controlled by the isolated cord, then one would expect that they would constrict as do the vessels in the fingers and toes However they behave as if the vaso constrictory influence of the isolated cord were overpowered by a vasodilator mechanism excited by the intact carotid sinus nerves or entirely under the control of higher centres In this connection it may be remembered that vasodilatation in the tongue was found following stimulation of the chorda tympany (Machol and Schlf 1928) and the Vidian nerve is thought to mediate vasodilator fibres for the nasal mucosa (Schlf 1937) Furthermore it must be pointed out that vasodilatation is a predominant function of the vasomotor apparatus in face neck and upper chest in man and more

over the patchy type of vasodilatation observed during bladder distension in patients with high cord lesions resembles the flushing elicited regularly by emotions in many normal subjects especially women We have further to consider the high blood pressure as a result of the vasoconstrictor response of the isolated cord to bladder distension in these high cord lesions The sudden rise in blood pressure no doubt leads as indicated by the visible engorgement of the temporal and supraclavicular vessels to a sudden increase in intracranial blood flow and mechanically to passive vasodilatation experienced by the patient as headache and head fullness and it seems safe to conclude that the passive vasodilatation must also play an important part in the vasodilator response of the cutaneous circulation in face neck upper chest and upper arms as well as in the nasal mucosal circulation

From a clinical point of view knowledge of these responses of autonomic mechanisms in paraplegic patients is important as these responses represent an alarm reaction of excessive activity of a viscus in the anæsthetic area of the body and they may be the only indicator of impending abdominal catastrophe On the other hand the awareness of some of these phenomena such as flushing feeling of heat *etc* can be utilized for the re education of the paralysed bladder and bowels and even sexual function

In all experiments on sweating the Quinizarin Method (L Guttmann) was used

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DISCUSSION

BURTON What startled me was the resemblance of this fantastic picture to what happens in the normal subject with amyl nitrite. There is this flushing of the head and neck and if one measures the finger

blood flow at the same time one finds it goes to zero I am interested in what you think of the idea that perhaps the whole of this unusual picture could be explained by release of acetylcholine or some very powerful vasodilator with the carotid sinus mechanism then coming in reacting to the change of blood pressure and thus producing the vaso constriction elsewhere?

GUTTMANN My experience suggests that this effect may be hormonal—whether it is acetylcholine or something else I do not know The question is through what pathway does it work? Here we have two possibilities either axon reflex through the carotid sinus and aorta or via posterior roots This type of vasodilatation in the face and neck reminds me of the effect of electrical stimulation of the peripheral end of a divided posterior root in man Here again as you know we are up against the same problem of whether the vasodilator effect is due to action of vasodilator fibres in the posterior roots or whether it is a hormonal effect I might remind you here of recent interesting findings by Hellauer in Germany and in this country by Holton They found vasodilator substances—Hellauer only in the posterior roots and Holton in both the posterior and anterior roots It is possible therefore if not probable that the vasodilator effects found in our experiments on visceral distension are of hormonal type

GRANT You mean the release within the paralysed parts is brought about by the circulation to the head and neck?

GUTTMANN The whole problem is even more complicated by the fact that you can get this patchy vasodilatation even in distal parts of the body Dr Cooper and Dr Kerslake will remember this occurrence in a boy with a complete lesion below C7 in whom there were two patches of vasodilatation occurring during the test one around the umbilicus and the other in the groins He was the first patient incidentally in whom I observed that this vasodilator effect does not occur only in the upper part of the body but in certain areas of the lower part of the body as a result of visceral distension in complete lesions of the spinal cord

DAWES I think I prefer the alternative explanation although it may not fit all the facts If you do assays on spinal cats giving saline intra venously from time to time it usually happens that after several hours the bladder begins to get full You notice this because there are then spontaneous rises of blood pressure this is the time to pass a catheter into the bladder and release the pressure there when the blood pressure becomes quite stable again I think this casual observation might fit in with your findings on man quite well and would explain the rise of blood pressure You might then expect to get as you suggest a carotid sinus or aortic depressor reflex which would account in part for the bradycardia *and possibly for the cervical vasodilatation I should have* thought this was the basis for the phenomenon although it may not explain all the facts

GUTTMANN Yes I do believe that the high blood pressure is one and probably the most important factor but I do not see that it explains everything *because we found that there was a vasodilatation* occurring in animals in whom the rise in blood pressure was not very high

EDHOLM Were the changes in blood pressure only observed in patients with high spinal lesions?

GUTTMANN Yes Because in a high lesion there is not much left of the vascular bed to compensate for changes in blood pressure

WEDDELL Is it a fact that if you cut the fifth nerve (leaving the sympathetic chain intact) you can no longer blush on that side of your face?

GUTTMANN I have no personal experience in man on this I did once divide the fifth anterior root in a man with an amputation in whom the posterior roots were functioning but I am afraid I did not study this phenomenon

DORNHORST I am not quite clear on the course of the sweating Do I understand it starts below the lesion and then subsequently appears in other parts?

GUTTMANN I think it starts below the level of the lesion as the segments there are often in a state of hyperactivity due to irritation produced by the post traumatic changes of the cord The whole research on sweating is extremely interesting We have come to the conclusion that there are two major sudomotor centres in the spinal cord One is in the cervico thoracic junction and the other is in the thoracico lumbar junction In a spinal transsection say at T3 or T4 the area which is stimulated more easily is the lowest part of that big convolution of cells situated in the cervico thoracic junction while in a lesion b low T6 the irritation of the pathological process affects more the proximal part of the distal sudomotor centre in the thoracico lumbar junction

DORNHORST It looks as though in spite of this very widespread sympathetic activity below the lesion there is no discharge of adrenaline if you get flushing above and a full bradycardiac response and a small pulse pressure

GUTTMANN I have thought about that but it does not explain why the vasodilatation occurs in the face neck and upper arms If discharge of adrenaline occurs as a result of visceral distension it would appear that it does not counteract the vasodilator effect in these areas

GRANT I think you told me yesterday that you had used transfusion in those cases Now if by transfusing these patients you increase their blood volume beyond the normal then you will increase the blood in the upper part of the body as well Does that produce any of these phenomena that you have seen?

GUTTMANN Not in the very acute stages

GRANT But when you transfuse them later?

GUTTMANN Yes in the later stages that is quite correct If you have a paraplegic with a chronic septic condition in the later stages blood transfusion is the normal technique used then you might get this phenomenon

HERTZMAN Do you get facial flushing with this bladder reflex at any level or is there a limit?

GUTTMANN The lowest level is T5 or T6 below that you do not get it

HERTZMAN That looks like a sympathetic dilator reflex

GUTTMANN But why is it so marked in the face and not in the lower parts of the body?

HERTZMAN Maybe there are no dilator fibres below That is the area where the sympathetic supply is dilator and not constrictor I think that perhaps interval observation could be made on vasomotor reactions in the skin

BARCROFT It seems to me to be a most interesting suggestion Dr Grant will recollect an experience of Sir Thomas Lewis on sympathectomized patients in whom he attempted to produce blushing If I remember rightly he could not get a patient who had been sympathectomized on one side to blush and he came to the conclusion that blushing was effected largely through the sympathetic mechanism If release of the sympathetic tone can make a person blush I wonder if it is conceivable that release of tone in the presence of such high blood pressure might produce a very great blush As Dr Hertzman suggested if the carotid sinus is working on the available sympathetic system and releasing the tone in the available upper part this might perhaps result in blushing

VON EULER Could the blushing be explained by a release of a sympathetic tone? I am thinking of the emotions such as what is sometimes called in psychiatry anger out That is to say that when people get excited and really angry they get a flushed face It would be hard to believe that that would be just due to a release of adrenaline It would rather point to the old idea that it is simply an activation of the dilator fibres The heart rate goes up a little and the blood pressure goes up What is the effect of ergotoxin or ergotamine on these patients? Will these influence this reaction in this upper part? In a small dose they will certainly not cause any blocking of the peripheral reflex The blood pressure after adrenaline will go up all right but it should not give the same amount of reflex action in the upper part if it were due to the action on the carotid sinus

GUTTMANN It is a very interesting suggestion which is worth trying

DORNHORST Would it be worth trying to block the stellate ganglion on one side and do this?

GUTTMANN Here we are up against the limitation of experiments in the spinal man Among other things for instance I have thought of injecting atropine we have not done it as we thought that it might just interfere with the last resources of vascular adaptation the organism has

GREENFIELD What about posture—is it feasible to tilt these people head down and so forth?

GUTTMANN We have studied the effects of posture on the cardiovascular system in the spinal man without bladder distension and this is a most important point In high thoracic and cervical lesions if you tilt the patients from the horizontal to the vertical positions they will faint in a very short time due to paralysis of splanchnic control What is most interesting is that this maladaptation to posture can be overcome by exercise In former times patients with high thoracic and cervical lesions were pushed about in spinal carriages in a lying position Now we are in a position to train the vasomotor control even in these high lesions We do this already in the early stages by frequent changes

of posture in bed The explanation is this change of posture produces distensions of the underlying vessels and sets up certain reflexes in the walls of the larger vessels resulting in vasoconstriction In other words the arterial vessels react to distension with contractions of their muscular walls like the viscera The effect of frequent change of posture in paraplegics is that such a patient can overcome postural hypotension and he can sit and stand in parallel bars without fainting These patients with high thoracic and cervical lesions can sit in their chairs move about and they even take part in sports To give an example last year when we had our first international Sports Day amongst our paraplegic patients they had amongst other sports events a competition in table tennis From the point of fairness I had to divide the patients into three groups the patients with cervical lesions had the greatest handicaps—the table tennis bat has to be fixed to their hands—then those with mid thoracic and low thoracic lesions The result was that in the doubles two men with cervical lesions—C6 and the other C7—beat all competitors with lower lesions! This shows to what extent training can overcome postural hypotension in the spinal man indeed an interesting example of applied physiology

SOME ASPECTS OF FUNCTIONAL DISORDERS OF THE CIRCULATION

P MARTIN

This conference has been of great value to those of us who are practising physicians and surgeons We stray so often from the rigid paths of physiology and anatomy that a sharp reminder such as this conference is of great value to us I can add very little of physiological or pathological interest but I shall ask a number of questions hoping that some time *in the future the physiologists will be able to answer them* for us and help us in the clinical aspects of Peripheral Vascular Disorders

We have been investigating cases at Hammersmith very fully with most of the methods which have been mentioned in this conference but we have come to the conclusion that, as a general rule they are not of great clinical help except possibly one or two of them

Firstly, the digital plethysmograph is a simple and easily applied piece of apparatus which not only gives us some indication of the response of the patients to reflex heating but also provides visual evidence in the shape of the curve as to the rigidity and resiliency of the digital arteries Even in a very elderly arteriosclerotic patient there is a marked increase in oscillations observable on reflex heating where there is no major vascular occlusion

Secondly the calf plethysmograph has been useful in showing improvement in the circulation particularly following some methods of arterial grafting The increase in blood flow to the calf following a period of exercise in the presence of arterial occlusion and the rapid return of the flow to normal is typical of a normal calf vasculature whereas where there is a major arterial obstruction the maximum flow achieved is

not so great and the return to normal is more prolonged After a grafting procedure the calf curve approximates to normal in cases which are successful We do not attach much importance to reflex heating or skin temperature changes except in so far as one limb may differ from its contralateral fellow

One of our greatest problems in cases exhibiting the Raynaud Phenomenon in the fingers is to choose those which will benefit from sympathectomy It seems to me a fair estimate that reports following cervical sympathectomy in the Raynaud Phenomenon indicate a recurrence rate of about 60 per cent These recurrences can be grouped into two classes firstly those that occur within four or five days and secondly those that recur after some months up to five years You may say that those cases which occur within four or five days have not been completely sympathectomized and that is so in a small number but in some that we have seen there has been no question of an incomplete sympathectomy and yet the Raynaud Phenomenon is as bad as ever before they are discharged from hospital It seems to us that in these cases a local fault in the vessel must be the cause Furthermore if we consider those cases of the Raynaud Phenomenon which occur as a result of trauma and particularly I shall consider for a moment trauma resulting from the use of vibrating tools it is the experience of most surgeons that a cervical sympathectomy does not improve the condition to any degree but that such cases are a true Raynaud Phenomenon with cold rather than vibration as the trigger is undoubted Similarly a Raynaud Phenomenon may occur in a finger following sepsis or bruising (such as has occurred following an injury from a Fives ball) and the Raynaud Phenomenon remains localized to the affected finger without involvement of any other part of the hand and is permanent In such cases it seems to me it would be difficult to blame anything but a local fault of the vessel As regards the late recurrences occurring from a few months up to five years the degree of recurrence of symptoms appears to run con

comitantly with the reappearance of sympathetic control In such cases either regeneration or more probably the activation of the ectopic ganglia described by Skoog and others is the important factor It is interesting to note that some of the best results of cervical sympathectomy for the Raynaud Phenomenon in the hand are obtained when this operation is performed for arteriosclerosis where it might be considered that a local factor was the primary cause but it is a fact that in such cases the results are good and as far as I can see much more permanent

When we consider sympathectomy of the lower limb I cannot agree with Dr Grant that recurrence is common and is associated with evidence of recurrent sympathetic activity In my experience the results of lumbar sympathectomy have always been good providing the lumbar sympathetic chain has been removed It does seem to me that there is no local factor which is operative in the toes and this I must admit is against the local theory operating in the hands but even so I believe there is sufficient evidence of some such factor in the upper limb

An important investigation which has not yet been carried out extensively would be to heat the trunk to such an extent that vasodilatation of the fingers occurs then subject the digits to local cold and find what their reaction would be Would a Raynaud Phenomenon develop? If it did surely this would be good evidence of a local fault in the artery If it did not then the anatomists and the physiologists must find for the surgeons some method of extirpating the sympathetic nerves responsible for each limb or alternatively they must find a drug which will achieve sympathetic paralysis Another exceedingly important point in my opinion is to determine whether it is in fact necessary to remove the stellate ganglion in sympathectomy procedures on the upper limb Removal of the stellate ganglion sometimes produces apart from a Horner s syndrome a distressing nasal obstruction in a number of cases due to engorgement of the nasal mucosa and sometimes a severe dandruff If

all three complications occur in a single patient which they sometimes do that patient is distinctly dissatisfied with the result of the operation although the vascular symptoms may be greatly improved Fortunately these side effects of the operation generally clear up after six to twelve months

This is one of the branches of surgery where we rely on the research of the physiologists anatomists and the pathologists and it is in recognition of their past services to the clinicians that I ask them again for their help in sorting out some of the problems I have mentioned today

DISCUSSION

HERTZMAN We have not an adequate series yet of the cases with stimulation of the upper thoracic ganglionic connections but one interesting point I can mention now is that the number of pre ganglionic sudomotors by way of T1 suggests that the conventional sympathectomy for the upper extremities does not give us an adequate interruption of preganglionics I offer that merely as a possibility Now it may be very difficult at times to elicit vasomotor reflexes and to provide the conditions under which a lively demonstration of vasomotor reflexes may be obtained Before one goes to such a facile possibility as a local fault theory it is vital to eliminate the possibility of vasomotor reflexes operating I think one of the big differences in the upper and lower extremities may be the greater ease of denervation of the lower extremity particularly the foot The upper extremity denervation appears to be very uncertain as for example when the conventional Smithwick operation is done At least we cannot harmonize claims in that direction with the results of stimulation

MARTIN The recently suggested operation is the conventional Smithwick plus stellate ganglionectomy plus removal of T4 and sometimes T5 The results of that as published by Smithwick have not affected the issue at all and the results still remain the same as in Telford s operation which was not a root section but was just a second and third preganglionic sympathectomy But if this more extensive operation is done there is a delay in the recurrence of symptoms of a year or so longer than there is if the sub total operation is done and there is a similar delay in the evidence of return of sympathetic activity We are very loath indeed to remove the stellate ganglion although I think there is some evidence that sometimes fibres go through it But if you do this operation Horner s syndrome is bitterly resented by many people The nasal obstruction which follows is a most serious disability to some people and they also get unilateral or bilateral dandruff of the hair You have only to see one patient with these troubles to appreciate their severity although there is a tendency for the nasal obstruction at least

to improve We are therefore most reluctant to be told that we have to remove this ganglion

GUTTMANN I would like to endorse Dr Martin s statement about how important it is to do sympathectomies as completely as possible I quite agree with him that the failure in Raynaud s disease is really due to incomplete sympathectomy I had several cases during the war of soldiers with Raynaud s disease and I remember in particular one man who had unilateral Raynaud s symptoms in the right hand The surgeon was quite convinced that he had done an extensive sympathec tomy but there was no improvement It was proved by the thermo regulatory sweat test that this sympathectomy was not complete It showed that the surgeon had done a very extensive sympathectomy for the face but not for the fingers where it was desired With regard to resection of the stellate ganglion I would like to ask Mr Martin whether the unpleasant results he mentioned are really permanent As far as my own and Professor Foerster s experience is concerned we always did peripheral sympathectomies including resection of the stellate ganglion It is quite true in the early stages immediately after the operation that there is complete blockage of the nasal passages but it wears off in most cases Even after a few days there is a return of air through the nostrils Were your cases permanent?

MARTIN *Yes I think some but not all cases certainly do improve* with time after a year or more It is a very trying year for everybody Curiously enough one of the things which is really horrible particularly to a fastidious woman is this unilateral scurf I do not know quite what scurf is but you do get it with anhydrosis of the scalp in some cases following sympathectomy and it seems to go on because anhydrosis persist Another rather interesting point is that if you get a recurrence of the Raynaud phenomenon following operation and do a second operation i e do a Smithwick the second time if you did a Telford the first time you get improvement of the symptoms with relapse again later That also seems to me to be fairly certain proof that regeneration is a factor and not only the local fault But the local fault I feel sure is also a factor although I don t like to bring in two separate mechanisms

GUTTMANN It might be that the most unpleasant permanent symptom after sympathectomy is the hyperhydrosis on the contra lateral sides of the face and on the border of the sympathectomy which I have de scribed as the border zone reaction This can indeed be very unpleasant especially in women If there is an extensive sympathectomy done in the lumbar or thoracic area you get bands of extreme hyperhydrosis over the trunk arms and face which are most disagreeable for the patient. This is one of the snags of sympathectomy

FITZGERALD I find that I am practically in total agreement with what Mr Martin has said from the surgical point of view and indeed from the point of view of what are our real problems I think that I might say however that my experience with the stellectomy operation has not been quite so bad as that which he related I do find myself rather more in agreement with what Dr Guttmann has said in regard to the disappearance of the adverse symptoms which undoubtedly do

follow sympathectomy Curiously enough I have had no difficulty whatsoever with this scalp trouble that one hears about On the contrary the eye condition has undoubtedly given rise to difficulty with some of my patients While the ophthalmologist assures me that the eye is in no way involved and that they have 6/6 vision and so forth the patients not infrequently assure me that their sight is dim on the operated side That has made me reluctant to do stellectomy operations if I can possibly avoid them Again I agree with what Dr Hertzman said about the difficulty of doing an adequate denervation of the upper limb and I feel that this is indeed very largely the reason why the results are so much worse on the upper than they are on the lower limb I think sufficient consideration has not been given to vertebral pathways which undoubtedly exist in these cases Possibly the solution of denervation of the upper limb might consist of a laminectomy operation and not an extra vertebral operation at all I think these pathways will come more and more into consideration and indeed have already done so from your own laboratories Dr Hertzman with Dr Kuntz haven t they?

HERTZMAN Under Dr Kuntz direction there has been a systematic dissection of the sympathetic trunk and of all its connections It is a long tedious job and it is impossible as yet to arrive at any statistically significant statement But there is an outstanding fact—accessory ganglia have been found all along from C8 through to about (I m not sure) L2 These ganglion cells are obviously cells displaced during the embryological development of the sympathetic system Sometimes the masses of them are incredible—I remember Dr Alexander had one ganglion that had a cell count of over 10 000 This ganglion was imbedded in the spinal nerve itself Now such a mass is capable of considerable functional activity The occurrence of these cells seems to be somewhat more frequent in the lower part than the upper part It is an open question as to whether or not these accessory pathways are of vital significance in control of the upper extremity We do not really know Of course one of our big problems has been that so many of our surgeons use sweating tests but what they are really interested in is vasomotor activity We have enough evidence at hand to indicate the unreliability of sweating tests for vasomotor innervation and *vice versa* There is some association certainly but how extensive it is still remains to be determined

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EDHOLM I have the unusual privilege as Chairman of having the first and the last word The Symposium has certainly been most successful in that it has aroused vigorous discussion One of the most important objects of a meeting of this kind is to get a number of people from many different centres to discuss their work so it can be seen where and why there may be disagreement and to clarify those areas of which we are ignorant

One aspect of the Symposium has been to demonstrate that we are still unable adequately to describe the architecture of the vascular

system The detailed arrangement of the anatomy and nerve supply of the small blood vessels in spite of so much work requires further study

The conditions in which observations are carried out have obviously a great effect on the results obtained The vascular system is remarkably labile and it is gradually becoming evident that a very vigorous control of the environment is essential in order to obtain reproducible results Artifacts abound although occasionally they also may be useful

I am unable to summarize the papers that you have heard Every one of them will be most rewarding to read in print I would like to express my thanks to you for the exciting experience it has been to act as your Chairman and to have had the privilege of listening not only to so many excellent papers but also to such good discussion

BARCROFT It is a very great pleasure and a great privilege for me to express on your behalf something which I know all of you feel most sincerely —the deepest gratitude to our Chairman and to the Ciba Foundation for these wonderful three days Perhaps this gratitude could be broken down into three separate portions Firstly I feel very strongly that the selection of those of us who are here has been most happy I know our Chairman has had a great deal to do with this and I think he would like me to say that Professor Dible too has been a great help and of course Dr Wolstenholme Secondly the actual meetings themselves which Dr Edholm has presided over have been wonderful examples of what such meetings should be Thirdly we will continue to feel grateful to him because of the stimulus we have received and because of the contacts which we shall hope to renew from time to time

Generalizing again therefore may I express on behalf of every one of us to Dr O G Edholm our Chairman our thanks for his notable contribution to the success of this twenty first this coming of age Symposium of the Ciba Foundation

AUTHOR INDEX

Plain numbers indicate a contribution by the author either in the form of a paper or to the discussions

Numbers in italics indicate a reference to the author s work

SUBJECT INDEX